The New England
Journal of Medicine

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VOLUME 223 DECEMBER 12, 1940 NUMBER 24

RELATION OF PYELONEPHRITIS AND OTHER URINARY-TRACT INFECTIONS TO ARTERIAL HYPERTENSION*

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ALTHOUGH as early as 1882 Wagner[1] described cases corresponding to pyelonephritis, and Göppert[2] in 1908 called attention to the frequency and occasional chronicity of "pyelitis," it is only in recent years that the natural history and clinical significance of pyelonephritis have been fully recognized. In America attention was called to certain aspects of this disease chiefly by Longcope,[3] Peters[4] and their associates. There are several reasons for this relatively slow recognition of the clinical characteristics of pyelonephritis. This disease has a strikingly variable clinical course and structural lesions. In the majority of cases the acute renal infection is benign and heals spontaneously, leaving behind only small renal scars. In others, however, the infection is chronic or recurrent, and the inflammatory tissue reaction gradually involves the entire kidney, unilaterally or bilaterally. Another characteristic of the disease, which has made the recognition of its natural history difficult, is the difference in the clinical features at various stages. Thus, whereas in the active infectious stage "pyuria" with symptoms of infection referable to the kidneys, ureter, bladder or urethra dominates the clinical picture, in the chronic, healed or healing stages symptoms of active infection and pyuria are often absent, and the clinical course is like that of chronic Bright's disease with arterial hypertension or renal failure.

During the last six years, we have studied a group of 100 patients suffering from pyelonephritis, with a detailed clinical and morphological investigation in various stages from the acute to the terminal chronic or healed. The results of this study together with the literature on the subject can be found elsewhere.[5] Since the publication of this report, additional selected cases have been studied. The purpose of this discussion is to summarize the present status of our knowledge in the light of personal experience.

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Presented before the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1940.

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STAGES OF PYELONEPHRITIS

We have classified pyelonephritis in four groups, according to the various stages of the disease: acute (pyelitis), chronic (active), healed and healed with recurrence. Acute pyelonephritis may heal, or may become chronic. Chronic pyelonephritis may persist or heal. Healed pyelonephritis may be followed by attacks of acute or chronic pyelonephritis. Each of these stages may occur either unilaterally or bilaterally.

This classification was made primarily on the basis of the combined clinical and histological evidence, but neither the specific causative organisms nor the mode of origin of the bacterial renal infection was taken into consideration. Such a relatively simple classification is justified because in most cases even the combined clinical, bacteriological and morphological evidence fails to reveal with any degree of certainty whether one is dealing with pyelonephritis of hematogenous (descending), urogenous (ascending) or lymphatic origin. We have not considered interstitial nephritis as pyelonephritis. Just as in other types of Bright's disease, without a detailed history including previous clinical studies, diagnosis of the various stages of pyelonephritis may be difficult.

The main morphologic characteristics of acute pyelonephritis consist in acute local or diffuse infection and inflammatory processes in the interstitial tissues, the tubules and the pelvis. In chronic and healed pyelonephritis, the main renal changes are as follows: inflammatory reaction with or without infection of the interstitial tissues; colloid casts

in the tubules, which are lined with atrophic epithelium; periglomerular fibrosis; evidence of infection or inflammation in the tubules; and frequently acute, subacute or chronic vascular lesions. The relative involvement of the interstitial tissues and tubules varies considerably from case to case. The clinical picture in the chronic stage is determined either by the vascular and the corresponding hypertensive elements, or by the disturbance of the excretory function of the kidney, depending on whether the interstitial tissues or the tubules are primarily affected.

Acute pyelonephritis. Acute pyelonephritis is the commonest disease of the kidneys. Its clinical features correspond to those recognized under the term, "pyelitis." In our experience the infection almost always involved the renal parenchyma as well as the pelvis, and hence "pyelitis" is a misnomer. The nature of the parenchymatous involvement is essentially the same, irrespective of the type or origin of the infection. Occasionally infection of the interstitial tissue without involvement of the nephron accounts for cases with all the systemic manifestations of the disease, including pain of renal origin, but without the characteristic urinary findings. Acute vascular lesions develop at times in the early stage of pyelonephritis, and it is of special interest that in some cases hyperplastic arteriolosclerosis developed within as short a time as six months after the onset of infection. Arterial hypertension, however, is usually absent in acute pyelonephritis. This observation is in harmony with previous conclusions that under certain circumstances severe obliterative arterial or arteriolar lesions may develop within as short a period as a month or two.

Chronic (active) pyelonephritis. In some persons renal infection with pyuria and bacteriuria may persist for months and years. The symptoms and other features referable to such chronic renal infection vary according to the severity and extensiveness of the infection and the degree of impairment of renal function. Arterial hypertension is frequently associated with this stage. Although the arterial hypertension is often severe (malignant) in contrast to other types of hypertension generalized atherosclerosis, cerebrovascular accidents, coronary disease and thrombosis are not prone to develop. Chronic pyelonephritis of childhood may be associated with general underdevelopment and changes in the bones. The cause of death, if it is related to the pyelonephritis, is usually uremia, vascular encephalopathy or heart failure.

Healed (diffuse) pyelonephritis. Healed (diffuse) pyelonephritis represents the healed or noninfectious stage of the acute or chronic (active) disease. Frequently the clinical diagnosis of this stage, particularly without a history of active infection in the past, is difficult or not feasible, because the clinical features closely resemble the terminal stage of benign or malignant nephrosclerosis (essential hypertension) or chronic glomerulonephritis. Since the majority of cases of acute pyelonephritis (pyelitis) heal, leaving behind small pyelonephritic scars, this type of healed focal pyelonephritis has no special clinical significance. This is also attested by the frequency of the "accidental" discovery of the scars during routine post-mortem examination. There are, on the other hand, an appreciable number of patients who, after suffering from chronic pyelonephritis or from repeated attacks of the acute form, apparently recover from the active infection but subsequently develop arterial hypertension, with or without renal failure. Clinical manifestations of active renal infection are lacking in these patients. There may be an increased number of white cells in the urine from time to time, but in many cases even repeated counts (Addis and Oliver[6]) fail to reveal abnormal elevations. If the hypertension is severe, showers of red blood cells may appear periodically in the urine. This phenomenon is due to ruptured capillaries or arterioles within the urinary passages. The pyelogram may show deformities of the pelvis, calyxes and ureters. Children or young adults suffering from persistent pyelonephritis may remain underdeveloped and may at times have changes, with deformities, in the bones or in the function of the glands of internal secretion. Frequently the bony abnormalities grossly resemble those seen in rickets, and hence are often said to be due to "renal rickets." In our experience, however, they do not correspond to the bony changes of true rickets as indicated by roentgenographical and histological evidence. Often they manifest themselves in increased or decreased density of the bones, and at times areas exhibiting both types of changes may be present within the same bone (Case 1).

Histologically, healed pyelonephritis is characterized by lymphocytic infiltration of the interstitial tissue and the pelvis and by colloid casts in the tubules. Mallory, Crane and Edwards[7] were able to reproduce this condition experimentally. Arterial hypertension is frequently associated with healed diffuse pyelonephritis, and it may develop long after the active infection, as indicated by clinical evidence, has healed. The inflammatory tissue reaction, precipitated by the infection, and hence the syndrome of hypertension, can advance long after the infection itself has subsided. The hypertension of healed pyelonephritis, which often dominates the clinical picture, is frequently severe and is manifested in headache, vertigo, vascular

crisis, pronounced changes in the eyegrounds and elevation of the spinal-fluid pressure, accompanied at times by increased protein content of the fluid. Elevation in the spinal-fluid pressure is prone to be associated with albuminuric retinitis, high diastolic pressure, cerebral encephalopathy and uremia. Cardiac asthma and other manifestations of left ventricular failure frequently occur. Atherosclerosis, coronary sclerosis and thrombosis, and cerebrovascular accidents, on the other hand, are seldom associated with this type of hypertension.

Healed pyelonephritis with recurrence. Patients with pyelonephritis are predisposed at times to recurrent attacks, due usually to anatomic abnormalities of the kidney or of the urinary passages, or

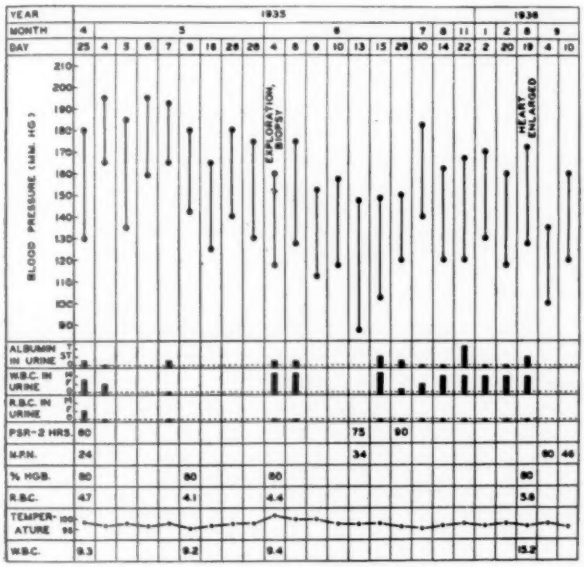

FIGURE 1. *Case 1.*
The clinical course of pyelonephritis.

to certain foci of infection. Such recurrences may develop after previous attacks of infection have healed. In these cases the clinical and histologic changes represent a combined picture of healed pyelonephritis and acute or chronic active pyelonephritis. The clinical diagnosis often depends on the availability of a history of past infections and of long infection-free periods.

The following two cases are reported as instructive examples of the natural history of pyelonephritis and the relation of urinary-tract infections to the development of arterial hypertension.

CASE 1. C. W. F. M., a 15-year-old schoolgirl, was admitted to the Peter Bent Brigham Hospital for the last time on January 26, 1940, with the complaint of fatigue, lethargy, anorexia and intermittent spasms of the limbs of 2 months' duration. The family history was irrelevant.

The present illness dated back to infancy, when between the ages of 6 months and 1 year the patient suffered from pneumonia and scarlet fever with otitis media. She was first observed in September, 1925, in another hospital, where the case was diagnosed as acute gastrointestinal intoxication and otitis media. In October, 1925, pyuria with a + test for albumin was first noted, and numerous white blood cells were found in the urine. Every urine specimen examined thereafter showed the presence of pus. A tonsillectomy and adenoidectomy were performed in 1932, at which time enuresis also was one of the symptoms. Since 1934, when the patient was 9, frequent and painful urination had been noted. In 1935 there were vomiting and intermittent abdominal pain.

Some of the clinical and laboratory findings from this date on are charted in Figures 1 and 2. The blood pressure at that time was 186/130. The kidney function was considerably reduced, the urea clearance being 19 per cent. The maximum specific gravity was 1.014. X-ray studies suggested a tumor of the right kidney, but surgical exploration failed to reveal one. A biopsy specimen of the right kidney five years before the patient's death revealed histologic changes characteristic of chronic pyelonephritis with thickening of the small arteries. The sections showed numerous pyelonephritic scars. Some of the tubules contained colloid casts; others were atrophic. The arteries within the scars showed productive endarteritis, and the arterioles hyperplastic arteriolosclerosis. There was considerable lymphocytic infiltration of the interstitial tissues. The glomeruli and the tubules in the nonscarred areas were essentially normal, whereas the blood vessels showed changes similar to but much less marked than those in the scarred areas. The pelvis was infiltrated with lymphocytes, plasma cells and occasional polymorphonuclear and eosinophilic leukocytes. In addition there were fairly numerous lymph follicles beneath the pelvic epithelium. The diagnosis of chronic pyelonephritis with pyuria, arterial hypertension and nephrosclerosis was made.

Following surgical recovery, the pyuria and the hypertension persisted, as indicated in Figure 1. The patient suffered from severe attacks of headache. Mandelic acid therapy failed to clear up the renal infection. In 1936 the aortic second sound became loud, and for the first time the heart was found to be enlarged. The patient showed only occasional and slight elevation of the temperature. Frequent analyses of the urine showed large numbers of white blood cells and on most occasions varying amounts of albumin. The specific gravity ranged between 1.017 and 1.020. A dilution-concentration test in August, 1936, showed a variation of only 1.001 and 1.012, and the urine culture showed a heavy growth of *Escherichia coli*. The blood hemoglobin was 12.5 gm. (74 per cent), and the red-cell count 5,620,000. The white-cell count was 15,250, with normal smear and differential. In September, 1936, the carbon dioxide combining power was 40 vol. per cent, and the nonprotein nitrogen 60 mg. per 100 cc. The results of the other laboratory investigations, including serological tests, were normal and noncontributory.

During 1937 her general condition remained satisfactory, although the arterial pressure was high and for the first time definite evidence of retinal arteriosclerosis was noted. In November, 1937, the patient developed profuse menstruation. At that time x-ray films of the kidney and bladder region failed to show the kidney outlines. There was a considerable degree of pyuria. In December the eyegrounds showed marked arteriovenous nicking and very early spots of degeneration of the retina. In February, 1938, bilateral pyelograms revealed definite deformities of both renal pelves, and the kidney outlines appeared to be quite small. The urine culture still showed *Esch.*

coli. The urine was of low specific gravity, with a slight trace of albumin, and the sediment continued to contain white blood cells. The vital capacity of the lungs was 2000 cc. In March, 1938, an increase in the severity of headaches was noted.

In May, 1938, the patient was again examined in the Peter Bent Brigham Hospital. No exudate, scars or hemorrhages of the retinas were observed. The heart sounds were somewhat accentuated, and both the aortic and pulmonary second sounds were quite loud. The rest of the

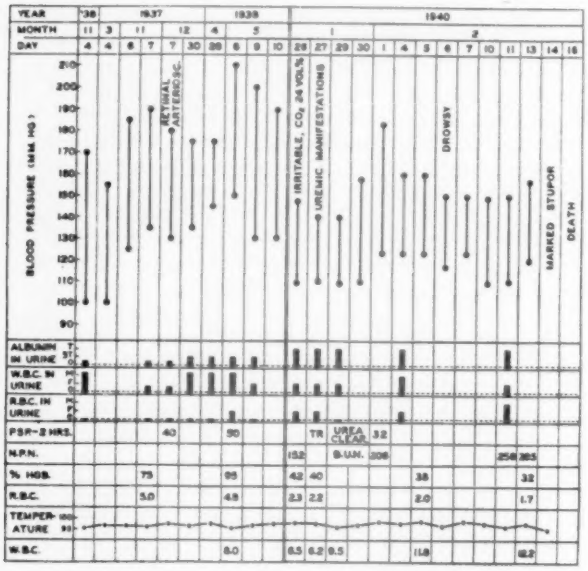

FIGURE 2. *Case 1 (continued).*
The later clinical course of pyelonephritis.

findings were irrelevant. In addition to the data presented in Figure 2, on two occasions the culture of the urine was sterile.

During 1939 the patient attended school regularly. In March, 1939, the school physician reported the blood pressure as 230/155 (not recorded in Fig. 2). In November the patient developed anorexia, became somewhat drowsy, and began to lose weight. She gradually developed increasing pallor and became irritable. Dyspnea appeared on exertion. In December, 1939, she developed cramping sensations in the fingers, hands, arms, feet and legs.

When admitted to the Peter Bent Brigham Hospital in January, 1940, the patient was thin and lethargic. Marked changes were present in the retinas of both eyes. There were numerous white patches over both fundi and an increase of physiologic cupping on the right. The arteries were tortuous and narrowed and showed increased light reflexes; no hemorrhages could be seen. The heart was enlarged. There was a presystolic gallop rhythm, and a blowing systolic murmur over the entire precordium. There were involuntary twitching movements of both arms and legs. Interference with venous return of the arms and legs precipitated carpopedal spasm. There was a generalized adenopathy in the cervical, axillary and inguinal regions. The rest of the examination was negative.

During her stay in the hospital the patient became increasingly apathetic. The breathing became deeper. On January 27 the carbon dioxide combining power was 24 vol. per cent, with the blood urea 158 mg. per 100 cc. A 7-foot film showed the heart to be above normal limits, with left ventricular hypertrophy. The lungs were clear. A kymogram showed regular and fairly active heart beats along the left border. The maximum systolic contraction was about 5 mm. Aortic pulsations were normal. The vital capacity of the lungs was 1450 cc. and later 1750 cc. Two electrocardiograms revealed prolonged QT interval (0.40 second) and an abnormal T wave in Lead 4.

X-ray films of the skull, spine, pelvis and long bones showed diffuse changes, with coarse mottling of some of the bones, — particularly in the cranial vault, — and with zones of increased density parallel to the vertebral plates, most marked in the lumbar vertebrae. There were no rachitic changes along the epiphyses, several of which were still visible. There were small concave areas of erosion in each humeral diaphysis close to the upper epiphysis.

On admission the hemoglobin was 40 per cent, the red-cell count 2,360,000. A smear indicated hypochromic anemia. The white-cell count was 6500. The blood Wassermann and Hinton tests were negative. The stool showed +++ guaiac and ++++ benzidine tests. The specific gravity of the urine varied between 1.012 and 1.014, with a trace of albumin and 2 to 12 white blood cells per high-power field. Finely, granular brown casts were present on several occasions. The urine cultures showed *Staphylococcus aureus* and *Aerobacter aerogenes*. The blood urea nitrogen gradually rose to 285 mg. per 100 cc. The total blood protein was 6.2 gm., the albumin 3.5 gm., and the globulin 2.7 gm. The blood calcium was 5.5 and 3.6 mg. per 100 cc. on two examinations; the phosphorus was 11.3 mg., and the chlorides 651 mg.

The patient lost 33 pounds in weight during the 21 days in the hospital. Soreness of the mouth and severe abdominal cramps developed. Later, soreness of the genitalia was the main complaint. She gradually lapsed into coma and died on February 15.

Autopsy. The pericardium contained 30 cc. of straw-colored fluid. The heart weighed 310 gm. The left ventricle was hypertrophied. The coronary arteries were normal. The kidneys were extremely small, the right weighing 25 and the left 30 gm., and were firm, reddish brown and finely granular, without retracting scars. The capsules stripped with difficulty. The cortices were only 1 mm. in thickness. The calyxes were greatly dilated and extended up to 1 or 2 mm. from the capsular surface. The ureters were moderately dilated, measuring 7 mm. in diameter. Constrictions were not observed, and the walls were not thickened. No ureteropelvic or ureterovesical valves were noted. The adrenal cortex contained a few small adenomas. The bladder was normal in size, with slight injection of the trigone. The rest of the examination failed to reveal pertinent findings.

On histologic examination the right kidney showed a rather diffuse increase in connective tissue. The scars were of varying ages. In the older scars the few persisting tubules contained colloid casts. The vascular changes were similar to those described in the biopsy specimen, obtained 5 years previously. In the more recently scarred areas, many of the tubules contained pus and showed abscess formation. The vessels in these areas showed a moderate degree of change. The nonscarred areas showed dilated tubules. The glomeruli were decreased in number and showed hypertrophy and various stages of alterative glomerulitis. The vascular changes were moderate. The pelvis showed marked infiltration of the subepithelial tissue with lymphocytes and plasma cells. The left kidney showed essentially the same picture. The mucosal surface of the bladder was completely denuded of epithelium. Throughout the submucosa there was considerable increase

in hyalinized connective tissue and lymphocytic cell infiltration. The parathyroid glands were greatly enlarged and composed primarily of cords of columns of sheath cells. Most of these cells had a dense eosinophilic to amphophilic type of cytoplasm. In a few areas the cells had a water-clear cytoplasm, were slightly enlarged and showed slight eccentricity in the position of the nuclei.

Case 2. H. E. B. S., a 45-year-old housewife, was admitted to the Peter Bent Brigham Hospital, April 22, 1940, with the chief complaints of headache for 6 weeks and nausea and vomiting for 2 days.

The illness dated back to January, 1921, when, during her first pregnancy, she developed acute pyelonephritis ("pyelitis") with frequency of urination and bilateral lumbar pain, more acute on the left. On examination there

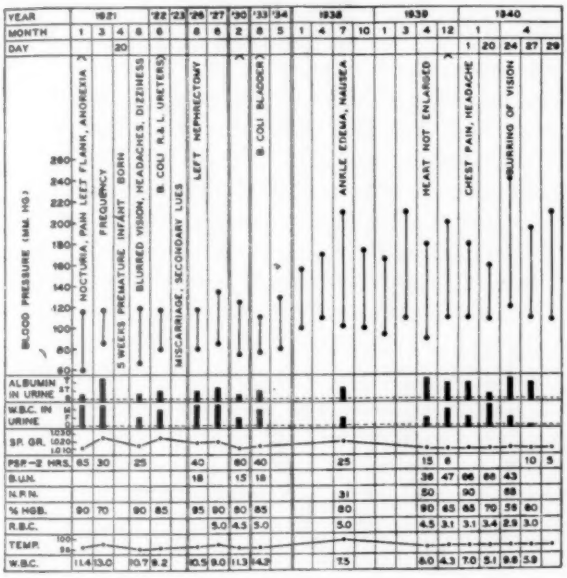

Figure 3. *Case 2.*

The clinical course of pyelonephritis. The "arrow heads" below the "day" *line indicate that the urine cultures were positive for* Escherichia coli.

was a systolic murmur, but as shown in Figure 3 the arterial pressure was normal. Cystoscopic examination failed to reveal evidence of cystitis. A specimen of urine obtained from the left ureter was hazy, and urine cultures from both the left and the right ureter yielded *Esch. coli.* The urine from the left ureter contained a large number of white blood cells. The phenolphthalein renal-function test was 65 per cent. The temperature during this hospital stay was essentially normal. The patient was discharged improved.

After discharge the urinary symptoms became aggravated, and the patient developed a low-grade fever. She was followed in the Outdoor Department and received pelvic lavage of the kidneys in February and March, 1921. At this time the urine showed a large trace of albumin, and the sediment contained many white blood cells. Following the birth of a 5-weeks-premature baby the urinary frequency continued, but the urine contained only a few white cells. There was marked costovertebral tenderness over the left lumbar area, and a slight degree over the right. In 1922 the patient felt fairly well, although she occasionally suffered from pain in the left flank. An increased number of white cells persisted in the urine. The results of the physical examinations were essentially negative. Ascending pyelograms revealed that the pelvic portion of the left kidney was rounded and the calyxes somewhat blunted. The right renal pelvis appeared to be larger and somewhat more irregular than the left. Cystoscopic examination failed to reveal evidence of cystitis. Cultures of the urine specimens obtained from each of the ureters yielded *Esch. coli.* There were numerous white cells in each of the catheter specimens. The specific gravity of the urine was 1.025. On this occasion the diagnosis of chronic pyelitis was made for the first time.

The patient had contracted syphilis following discharge from the hospital, and a blood Wassermann test became positive. She received antisyphilitic treatment. In 1925 the pain in the left upper quadrant and the pyuria returned. During February, 1926, she had chills and fever on an average of once a week, and later the pain in the left loin became accentuated. In August, 1926, there were tenderness and a questionable mass in the region of the left kidney. The blood pressure was still normal. At this time cystoscopy failed again to reveal evidence of cystitis. The orifice of the left ureter was slightly reddened. The catheter passed easily to the right pelvis. The urine obtained on the right was clear, and the culture sterile. A pyelogram on the right indicated a slightly dilated pelvis and rounded calyxes. The dye appeared at the end of the catheter in 5 minutes. The catheter introduced into the left ureter passed only a distance of 6.5 cm. The urine collected was cloudy, and the culture yielded *Esch. coli.*

On September 1, 1926, a left nephrectomy was performed by Dr. William C. Quinby. The kidney was very small, measuring 7 by 5.5 cm., and was 3 cm. thick. The pelvis was dilated. Very little kidney substance was seen. A small quantity of puriform material could be squeezed out of the tissues. Histologic examination showed focal scars due to healed pyelonephritis, as evidenced by the presence of colloid casts, periglomerular fibrosis and interstitial infiltration with lymphocytes. In these scars the arteries showed a rather marked degree of proliferative endarteritis, and the arterioles hyperplastic arteriolosclerosis. In the unaffected areas the renal tissue was essentially normal, and the blood vessels showed no changes of any significance. In the connective tissue beneath the pelvic epithelium were numerous lymphocytes and plasma cells and a moderate number of eosinophils and polymorphonuclear leukocytes. In addition there were lymph follicles with active germinal centers. The diagnoses were healed pyelonephritis, with some activity in the pelvis, and probable congenital hypoplastic kidney.

Following nephrectomy the patient improved, although she re-entered the hospital in June, 1927, with symptoms suggestive of chronic endocervicitis. She was quite well from this time until January, 1930, when she developed sudden and severe pain in the right flank, followed by nocturia (eight or ten times). Examination showed marked tenderness in the right flank; the right kidney was palpable. Cystoscopic examination showed considerable reddening of the mucosa of the bladder. The right ureteral opening showed some edema about the orifice. The phenolphthalein output of the kidney was 60 per cent. During the hospital stay urine specimens from the right ureter were obtained on three occasions, and the culture of each yielded *Esch. coli.* The urine contained a slight trace of albumin and many white cells. A blood Wassermann test was positive. The blood pressure was still normal. The diagnosis made was recurrent acute pyelitis. For 3 years thereafter, the patient had complete relief from renal and urinary symptoms, but in 1933 she

developed pain in the right upper quadrant radiating to the interscapular region. Icterus of the scleras had been observed at times. In August, 1933, physical examination was essentially normal. The cholecystogram revealed a normal gall bladder. Cystoscopic examination and the urine sediment obtained from the right ureter were normal, but culture of the urine yielded *Esch. coli*. The other laboratory findings were essentially unchanged.

In 1938 the patient again entered the hospital, complaining of pain in the right flank, chills and fever. For the first time she suffered from dizzy spells and swelling of the ankles. The physical examination was essentially normal. The blood pressure was elevated. On cystoscopic examination the bladder was normal. An intravenous urogram failed to show any definite excretion. The urine specimen obtained from the right ureter was sterile. The patient improved and was discharged from the hospital. In 1939 she developed pain in the left breast, and also began to experience attacks of dizziness and weakness. On examination the eyegrounds were normal except for slight arteriovenous nicking. The heart was normal. The palpable arteries were not thickened. The rest of the examination was negative. The blood pressure was elevated (Fig. 3). The vital capacity of the lungs was 2100 cc. A 7-foot film of the heart indicated that the size was just within normal limits. The electrocardiogram was normal except for left-axis deviation. Renal tests indicated lowered function. It is of interest that the white-cell count in the urine was not elevated on repeated examination. The discharge diagnosis in May, 1939, was pyelonephritis with arterial hypertension. On numerous occasions after discharge the patient experienced thoracic pain, with radiation down the left arm; this was brought on by slight exertion and by emotional distress. In addition the pain in the right flank, accompanied by nocturia and pyuria, became severe. Repeated examination of the urine in the Outdoor Department revealed persistent albuminuria and pyuria. In December, 1939, the patient developed constant nausea and frequent attacks of vomiting associated with headache and dizziness. Examination revealed slight arteriovenous nicking of the vessels of the eyegrounds and moderate enlargement of the heart. A split second sound was present with a systolic murmur. Exquisite tenderness was present over the right flank posteriorly. Other data obtained are presented in Figure 3. The urine showed increased white cells, and the culture yielded *Esch. coli*. X-ray films failed to reveal the outline of the right kidney or the presence of stones. The electrocardiogram remained as before. The patient was discharged in January, 1940, in an improved state.

In March, 1940, the severe throbbing headache returned, and in April the pain in the right flank again became severer. The patient was nauseated, and vomited on several occasions. She also experienced palpitation and sensations of constriction in the substernal region, accompanied by increasing weakness. The results of the examination during hospitalization were essentially unchanged, with a few exceptions. The systolic murmur was more pronounced. The arterial pressure was higher, For the first time several fresh linear hemorrhages and an increase in the light reflex of the arteries of the eyegrounds were observed. The arteries were narrow and varied in caliber. The dynamics and chemical constituents of the spinal fluid were normal. Urine cultures revealed *Staph. aureus* in small numbers, and in one specimen nonhemolytic enterococci. Other pertinent data are presented in Figure 3. After discharge from the hospital, the patient was last seen in July, 1940, when the symptoms were mainly cardiac and hypertensive in origin.

These two cases are instructive in demonstrating the clinical course of the severe form of pyelonephritis. In Case 1 the renal infection started at the age of six months, and persisted until the death of the patient at fifteen years. Whereas local symptoms with pyuria dominated the clinical picture in early childhood, Bright's disease with arterial hypertension was the presenting syndrome during the last two years. The cause of death was uremia, and at the time of death the renal infection still persisted. Hence the case represents chronic (active) pyelonephritis. The kidneys at post-mortem examination were unusually small, but without congenital abnormalities. In our opinion this type of kidney is caused by lack of normal growth due to chronic infection, rather than by contraction of the kidney.

Case 2 represents the late effects of pyelonephritis in adult life. In this patient the first attack developed during pregnancy. The left kidney, removed surgically, was small and probably congenitally hypoplastic. Whether the right kidney has any congenital malformation cannot be stated with certainty. During the twenty years that this patient has been studied, she has suffered from repeated attacks of acute infection, suggesting healed and recurrent pyelonephritis. The gradual onset of hypertension is clearly demonstrated in this case. For the first seventeen years, symptoms referable to the urinary system and pyuria were the main features, and the blood pressure was normal. Symptoms of severe hypertension, with changes in the eyegrounds, and angina pectoris developed during the last three years.

Vascular Changes and the Arterial Hypertension of Pyelonephritis

In acute pyelonephritis the inflammatory tissue reaction may at times involve the renal arterioles and venules. In the cases we observed, such lesions usually consisted of a deposition of fibrin in the wall of an arteriole and of infiltration of polymorphonuclear leukocytes and mononuclear cells. At times partial or complete thrombosis of the vascular lumen or proliferation of the endothelium developed.

In chronic or healed pyelonephritis, vascular lesions in the kidneys are often prominent, involving both the interarcuate renal arteries and the arterioles. In the arteries there is increased connective tissue in the intima. The internal elastic membrane is frequently duplicated. The walls of the arterioles are thickened as a result of concentric proliferation of the cells (hyperplastic arteriolosclerosis). Hyalinization of the arterioles develops only rarely. Arteriolar necrosis and acute

arteriolitis resembling periarteritis nodosa also occur in some cases. It is of interest that in cases of cystitis, hydronephrosis and renal tuberculosis, uncomplicated by pyelonephritis, vascular changes and hypertension did not occur. These morbid states, as well as infections of the urethra or of the bladder, are not responsible, as a rule, for hypertension. The presence of deformities of the renal pelvis and of the ureters in patients with arterial hypertension does not justify, per se, the conclusion that it bears a causative relation to the renal origin of hypertension. In many cases the changes in the urinary passages are but incidental findings in persons with "primary" nephrosclerosis. This has not been taken into consideration by some investigators. A relation was found between arterial hypertension and the severity and diffuseness of the obliterative vascular lesions caused by pyelonephritis. On the other hand, a close correlation between arterial hypertension and the size or the functional capacity of the kidneys was not noted. Thus the kidney in chronic or healed pyelonephritis may be normal in size, and yet insufficient because of the obstructed tubules.

Our studies indicate that the vascular changes in pyelonephritis are proliferative rather than degenerative. Because in focal pyelonephritis the vascular changes are usually localized within areas corresponding to the inflammatory tissue reactions, and because in unilateral pyelonephritis, without long-persisting arterial hypertension, the vascular changes are present only in the affected kidney, we concluded that the vascular changes are caused primarily by the inflammatory tissue reactions of pyelonephritis and not by hypertension. This concept is supported also by the fact that a moderate degree of diffuse arteriolar change is present without, and presumably before, the development of hypertension. However, because in unilateral pyelonephritis with severe hypertension some arteriolar lesions subsequently develop in the unaffected kidney, hypertension is thought to be an accelerating or intensifying factor. Thus in the development of vascular changes we are dealing with a vicious circle precipitated by pyelonephritis and, in turn, accentuated and accelerated by hypertension. The specific factors suspected of being responsible for the vascular lesions observed in pyelonephritis are slow blood flow, intravascular pressure and local edema of the vessels. Thus the mechanism of the development and the morphologic characteristics of these renal vascular lesions are not unlike those of the lesions in the lungs in certain cases of mitral stenosis.[8] Similar types of vascular lesions were also observed in a variety of conditions, as either a systemic or a localized vascular response to certain noxious stimuli: they may be present in carcinomatous lymphangitis or in emphysema of the lungs, and around gastric and duodenal ulcers, indicating that not infection but inflammation is the essential factor for the development of these proliferative vascular lesions. Because the vascular lesions in pyelonephritis are highly proliferative and are similar to those found in the usual type of malignant nephrosclerosis, there is a great tendency in chronic or healed pyelonephritis to severe renal ischemia and hence to severe hypertension. It has been estimated that pyelonephritis is responsible for 15 to 20 per cent of all cases of malignant hypertension.

Of 20 autopsied cases with unilateral chronic or healed pyelonephritis the blood pressure had been normal in only 8. The size of the affected kidney was usually greatly diminished, whereas the unaffected kidney was often enlarged. The vascular changes in the affected kidney in cases with normal blood pressure varied from moderate to severe, with the unaffected kidney showing no appreciable changes. In cases of hypertension the affected kidney showed marked vascular changes, and the unaffected side showed slight to moderate changes.

In one group of patients with chronic or healed pyelonephritis the kidneys were unusually small. In our experience the smallest kidneys in cases of chronic Bright's disease were those caused by pyelonephritis. In several of these, no abnormalities of the pelvis, ureter, bladder or urethra were found. The blood pressure in most cases was very high, but in others only slightly elevated. The evidence we gathered indicates that renal infection beginning in early childhood with resultant scarring that interferes with normal renal growth can account for the markedly reduced size of the kidney. It is probable, however, that congenital hypoplastic or so-called "hypogenetic" kidneys, particularly if they are associated with congenital malformation of the urinary passages, predispose to chronic pyelonephritis; and a combination of such congenital renal malformation with pyelonephritis is responsible in some cases for such unusually small kidneys. Some clinicopathological correlation suggests that congenital hypoplastic or hypogenetic kidneys even without complicating pyelonephritis may eventually lead to uremia. Obviously these small kidneys are not "primary" or "secondarily contracted," but are the result of a lack of physiologic growth. The rapidly increasing discrepancy between the size and function of the body and that of the kidneys leads finally to uremia, usually in early adult life.

Pyelonephritis and Toxemia of Pregnancy

The interrelation between pyelonephritis and toxemia of pregnancy deserves special consideration. In our experience acute pyelonephritis (pyelitis) per se is usually not responsible for toxemia of pregnancy. It is of interest, on the other hand, that in a group of 8 women with arterial hypertension and with small chronic or healed pyelonephritic kidneys post mortem, 6 had had attacks of toxemia. In a recent study of toxemia of pregnancy ("the vascular syndrome of pregnancy") we[9] concluded that, although the average incidence of toxemia of pregnancy was 3 per cent in all cases of pregnancy, in patients with pre-existing arterial hypertension, not considering the specific etiology, it was 50 per cent. It is probable that in a group of patients with chronic or healed pyelonephritis associated with hypertension and with low-reserve kidneys, the incidence of toxemia will be found even higher. In spite of this high incidence, in the *total group* of toxemias pyelonephritis plays a relatively small role. Thus in a group of 60 cases studied clinically only 3 patients had chronic pyelonephritis associated with prepregnant hypertension. Similarly in a group of 26 autopsied cases with fatal eclampsia, there was but 1 of chronic pyelonephritis. The fact that, in a large group of patients with toxemia, acute "pyelitis" frequently occurs does not necessarily indicate a causative correlation between the two conditions. Thus in our experience bacteriuria occurred in 20 per cent of the normal pregnancies. The syndrome of toxemia and the characteristics of its hypertension are different from those of pyelonephritis. Toxemia superimposed on chronic pyelonephritis is therefore not a mere accentuation of the pre-existing hypertension, but represents the development of another morbid state, which frequently occurs without previous hypertension or renal disease.

Pyelonephritis and Bright's Disease

The fact that pyelonephritis can lead not only to renal failure, but also to vascular lesions and to arterial hypertension long after the disappearance of bacterial infection, indicates that in its chronic or healed stage it should be considered as one form of Bright's disease. Although acute pyelonephritis is the most frequent disease of the kidney, chronic pyelonephritis and diffuse healed pyelonephritis are also important renal diseases. Their relative role can be estimated from an analysis of 55 cases with small contracted kidneys. In this group the etiology of chronic Bright's disease was nephrosclerosis in 27 cases, pyelonephritis in 18 and glomerulonephritis in 10. Thus pyelonephritis is oftener responsible for small contracted kidneys than is glomerulonephritis.

Treatment

The principle involved in the treatment of pyelonephritis necessitates the application of measures to relieve or improve stasis of the urinary flow in any part of the tract from the glomerulus to the urethra, and to interfere with the growth or multiplication of the causative organisms. In many cases the *chemical agent* used simply acts indirectly to intensify the immunologic reactions in the blood and tissues. The reaction of organisms to chemical substances in vitro does not justify conclusions as to their clinical efficacy. Many erroneous statements as to the value of urinary antiseptics have been based on such faulty assumptions. Thus mandelic acid is a bactericidal and a relatively better bacteriostatic agent than sulfanilamide for *Esch. coli* in vitro; and yet the latter is often more effective in the treatment of acute pyelonephritis caused by *Esch. coli.*

The natural history of pyelonephritis indicates that to be effective treatment should be instituted in the early acute stage of the disease. Not only do the progressive structural changes create a more favorable habitat for the bacteria, but in the subacute and in the chronic stage the surgical and chemical measures become less effective. Further, once the infection has reached a certain stage, the inflammatory tissue reactions often continue to advance long after the organisms have been eradicated. Thus hypertensive Bright's disease frequently develops during the bacteria-free stage.

Cases of successful abolition of arterial hypertension following *surgical removal of unilaterally diseased kidneys* are appearing in increasing numbers, but the follow-up period of the cases operated on is too short to warrant a final expression of opinion. It should be emphasized that the clinical diagnosis of unilateral renal ischemia is difficult. Systematic clinical study of the size and physiologic state of both the kidneys and the urinary passages is essential before surgical operation is undertaken. Mistaken diagnoses and inadequate consideration have been responsible for many fatalities.

Although in recent years great advances have been made in the study of pyelonephritis, this very progress has raised several new problems. Whereas it is recognized that the colon bacillus and the staphylococcus are the commonest causes of bacterial infection of the kidneys, a number of other bacteria may induce suppurative renal processes. Streptococcal infections often predispose to the subsequent development of *Esch. coli* pyelonephritis. At times, however, these and other bacteria

are found in the urine without pyuria. Are these cases of "silent bacteriurias" benign, or can they cause subsequent hypertension or renal failure? Should they be treated as intensely as those associated with the clinical picture of pyelonephritis? What are the factors that predispose one patient and not another to severe vascular lesions and hypertension? Are the renal vessels of some persons inherently more resistant to inflammatory tissue reaction than those of others? These and other questions cannot be answered at present.

Summary

The clinical course of pyelonephritis varies considerably. Whereas in most cases the disease is benign and self-limiting, at times it becomes chronic, leading to arterial hypertension and to renal or cardiac insufficiency.

Pyelonephritis has been classified in four groups: acute (pyelitis), chronic (active), healed and healed with recurrence.

Two cases are reported as instructive examples of the natural history of pyelonephritis and of the relation of urinary-tract infections to the development of arterial hypertension. In Case 1 the renal infection started when the patient was six months old, and persisted until her death at the age of fifteen years. Although the local symptoms with pyuria dominated the clinical picture in early childhood, Bright's disease with arterial hypertension was the presenting syndrome during the last two years. The cause of death was uremia. In Case 2 healed pyelonephritis with recurrence caused by *Esch. coli* started during pregnancy at the age of twenty-five, and for twenty years thereafter numerous attacks occurred, leading to severe hypertension and angina pectoris.

Tuberculosis of the kidneys, infections of the renal pelvis, hydronephrosis and cystitis are usually not responsible for arterial hypertension.

Children with low-reserve kidneys of years' duration caused by pyelonephritis may have disturbances of bone formation with deformities (renal rickets), but the characteristics of these changes differ from those of true rickets.

Acute pyelonephritis (pyelitis) per se is usually not responsible for toxemia of pregnancy. It has an indirect relation to toxemia and eclampsia so far as it predisposes to arterial hypertension and to low-reserve kidneys.

Diffuse pyelonephritis in its chronic or healed stage should be considered as one form of Bright's disease.

The principles involved in the treatment and prevention of pyelonephritis are discussed.

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OPEN-AIR SANATORIUM CARE FOR PATIENTS WITH RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE*

Preliminary Report

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BOSTON

THE purpose of this paper is to review briefly, as a preliminary report, the experience of two years in caring for a small group of children with rheumatic fever in an open-air sanatorium in the rigorous climate of Boston. This has been an experiment, arising from the facts, increasingly apparent, that rheumatic fever is widespread among undernourished children crowded together in unhealthful environments and that provision for their care is altogether inadequate.

THE EXPERIMENT

In the fall of 1938, at the suggestion of Dr. Kenneth Blackfan, the Sharon Sanatorium, which is just outside Boston, made available for the care of children with rheumatic fever a pavilion previously used as a preventorium for tuberculosis. The capacity of the building is ten boys and ten girls. The children have been selected from the Children's Hospital. Their placement has been financed in part by The Children's Mission to Children and in part by the sanatorium. Primarily this has been an experiment in hospitalization based on an attempt to determine whether a rheumatic child in a carefully controlled, open-air environment can be kept free of respiratory infections, and whether the infection itself responds favorably to such an environment.

During the winter of 1938-1939, 20 children who had recently recovered from active rheumatic fever were sent to the sanatorium. Whenever possible, they were admitted following the first attack. Some had respiratory infections at the time of admission, but all were free from active rheumatic infection. They entered in the fall and remained as a closed colony during the winter and spring months. There was careful restriction in regard to visitors. Only the child's parents were allowed to visit, one afternoon a week. All visitors were required to wear masks, and no one with a cold, sore throat or other infection was permitted near the building. Emphasis was placed on education of the children, so that on returning home they were able to continue with their proper grades in school. A full-time occupational therapist was available to keep them happy and busy when they were not at their schoolwork. The children slept outdoors, even in the severest weather, and were kept in the open air as much as possible during the day.

Throughout the winter all the children remained free from respiratory infections, and recurrences of rheumatic fever (Fig. 1). During the summer of 1939, 15 children were discharged, the rest being kept for further care. The discharged children have been followed by the Rheumatic Fever Clinic at the Children's Hospital for an average period of over a year. Since returning home from the sanatorium, some of them have developed respiratory infections and other minor ailments, but none have had recurrences of rheumatic fever or evidence of increased heart disease.

With this experience as a background, a change in policy was made during the following winter. Only children with active rheumatic infection were placed. Some of them had rather severe rheumatic fever and heart disease. Furthermore, the policy of maintaining a closed colony was abandoned, and children were admitted as beds became available. The only restrictions in the selection of patients were that they should have well-established disease, and be between the ages of five and twelve years, free from chorea and free from heart failure. These restrictions were considered necessary because of the limited nursing service and, in the case of heart failure, because of limited medical supervision.

During the second year 28 children were admitted. The course of their disease was followed by clinical observation, more specifically by that of temperature, sleeping pulse rate and gain in weight, and determinations of the erythrocyte-sedimentation rate. When shown to be free of all evidence of active infection, they were allowed a gradual increase in activity for two months, when they were permitted full activity. Instead of being sent home at this time, they were kept for a further period of a few months, during which it was hoped that they would overcome any latent rheumatic infection and attain a state

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of vigorous health, to enable them to withstand the rigors of their home environment, which was probably poor at best.

The results during the second year were as completely satisfactory as those during the first. During the second winter the children remained free of respiratory infections except for one or two minor head colds. Of greater significance was the absence of recurrent rheumatic infection in any case (Fig. 2). This was all the more gratifying

Another feature that has most impressed those who have watched these children from week to week is their steady uninterrupted gain in general health. This is difficult to demonstrate with factual data. It is reflected in part by their gain in weight, which is a sign that convalescence is progressing satisfactorily (Fig. 3).

During the second year, to study further the factors that might have contributed to the freedom from infection within the group, cultures were

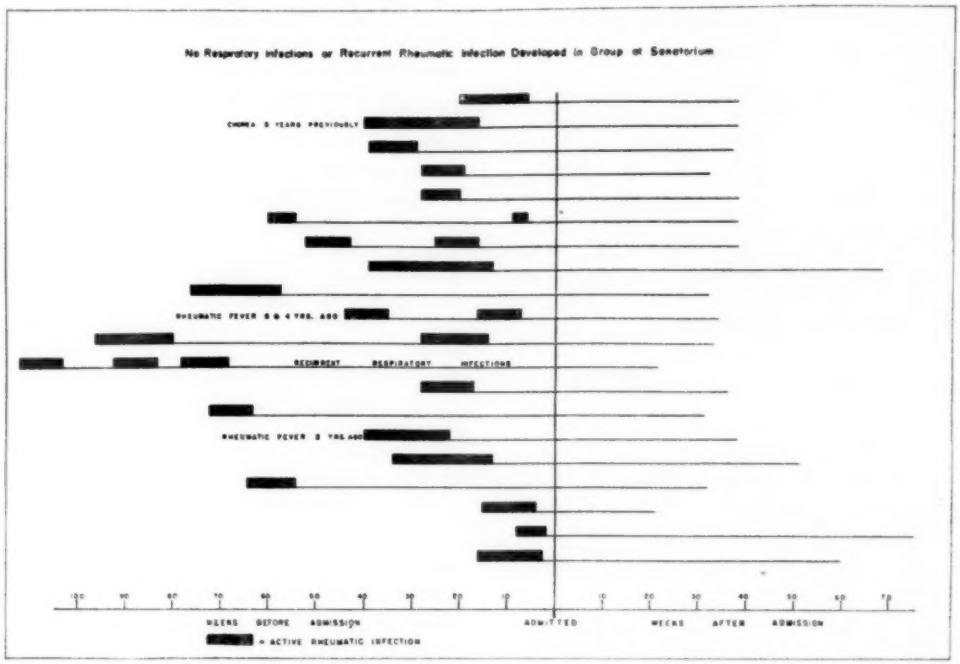
No Respiratory Infections or Recurrent Rheumatic Infection Developed in Group at Sanatorium
CHOREA 5 YEARS PREVIOUSLY
RHEUMATIC FEVER 6 & 4 YRS. AGO
RECURRENT RESPIRATORY INFECTIONS
RHEUMATIC FEVER 3 YRS. AGO
WEEKS BEFORE ADMISSION
ADMITTED
WEEKS AFTER ADMISSION
= ACTIVE RHEUMATIC INFECTION

FIGURE 1.

The courses of the first 20 rheumatic children at the sanatorium, showing periods of active infection before admission, freedom from active infection on admission and freedom from active infection following admission.

because the children had varying degrees of active infection on admission, and hence were sicker than those in the first group, who had already recovered from their active infection.

As stated above, children with congestive heart failure have not been considered suitable for the present facilities of the sanatorium. In one child heart failure developed between the time she was accepted at the clinic and her admission. She represented the overwhelming, rapidly progressive form of rheumatic heart disease, from which she died after having been sent back to the hospital. Obviously no claim is made that a progressive course such as this can in any way be influenced by one form of hospitalization in contrast to another. This in no way detracts from the value of the sanatorium experience, the essential feature of which is the freedom, to date, from respiratory infection and recurrent rheumatic fever.

taken regularly from the children's throats and repeatedly from samples of the air. A considerable number of hemolytic streptococci have been obtained from the throat cultures; since the typing of these is not finished, the results are not reported here, but will be included in a more complete presentation of this work at a later date. The cultures of the air have been helpful in giving bacteriological evidence to support the value of the open-air environment. With freely circulating air that is rapidly diluted with the outer air there is relative freedom from bacterial contamination in comparison with the usual hospital wards. This is illustrated by Figure 4, which is taken from the work of Fé del Mundo and McKhann.[1] By means of the Wells[2] centrifuge apparatus, estimations have been made of the number of bacteria per 10 cubic feet of air. Repeated determinations were made during the winter, spring and summer under

varying conditions. The bacterial counts obtained in this manner compared favorably with similar counts obtained in a very carefully supervised, air-conditioned, infection-free premature nursery and in infant cubicles protected with ultra-violet radiation. The counts taken from hospital wards and waiting-rooms showed a much greater bacterial contamination. Also of considerable significance is the fact that hemolytic streptococci and other pathogenic bacteria were found in the samples from the hospital wards, whereas only staphylococci, molds and a variety of nonpathogenic organisms were obtained at the sanatorium.

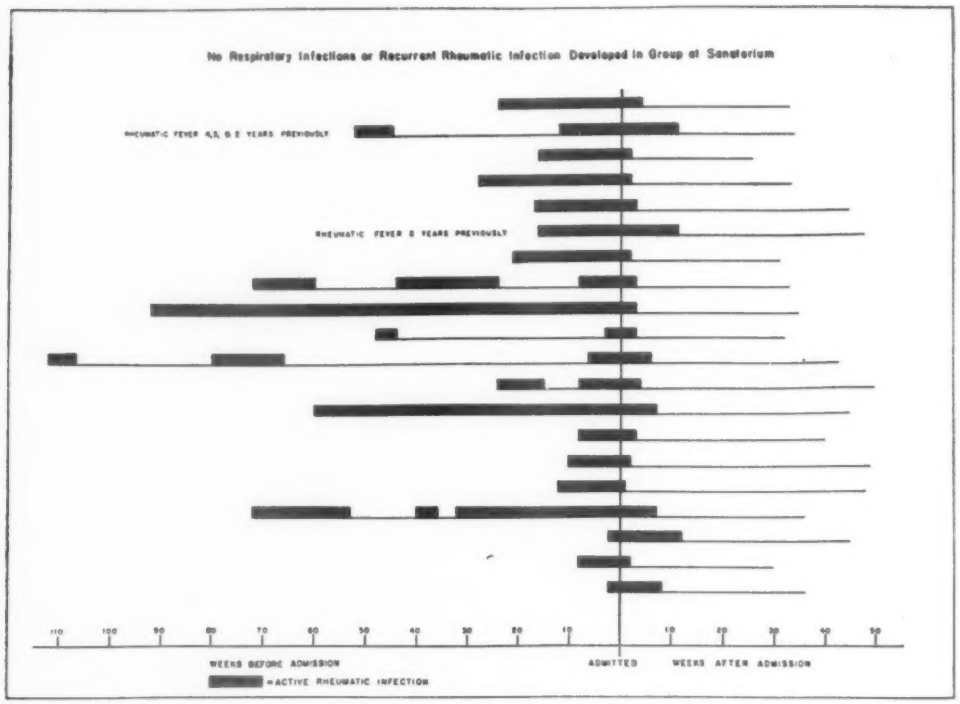
No Respiratory Infections or Recurrent Rheumatic Infection Developed in Group at Sanatorium
RHEUMATIC FEVER 4,3, 0 2 YEARS PREVIOUSLY
RHEUMATIC FEVER 0 YEARS PREVIOUSLY
110 100 90 80 70 60 50 40 30 20 10 0 10 20 30 40 50
WEEKS BEFORE ADMISSION
ADMITTED
WEEKS AFTER ADMISSION
= ACTIVE RHEUMATIC INFECTION

FIGURE 2.

The courses of the second 20 rheumatic children at the sanatorium, showing active infection before and on admission and freedom from active infection following admission.

DISCUSSION

It would be premature at present to attempt to analyze too closely the results of this experiment. The time has been short, and the number of cases limited. Many features must be further analyzed. Among these may be mentioned the open-air environment, the small size of the group, the strict control of visitors, the small personnel coming in contact with the children, the optimal diet and the careful regulation of the activities of each child. Rheumatic fever being a chronic and recurrent disease, it will probably be several years before conclusive statements can be made in regard to the value of these factors. In the meantime, this type of care deserves continued trial, particularly since the very real problem of the most suitable management for the rheumatic child is now receiving considerable attention. Appreciation of this problem has resulted, on the one hand, from an increasing recognition of the prevalence and severity of the disease, and on the other, from a growing realization of the lack of facilities now available for its proper care.

The incidence of rheumatic fever is difficult to determine, since it is not a reportable disease and hence does not appear in the community vital statistics. Recently in Boston a laborious case-finding study[3] revealed that 900 new cases of rheumatic fever, or rheumatic heart disease, occur each year within the city limits. For the same period and in the same area, there were 878 new cases of pulmonary tuberculosis.[4]

The severity of the disease is made all too apparent by the frequency with which it causes heart damage or death. Bland and Jones[5] have shown that in a series of 1000 cases followed for an average of over ten years, 426 patients had varying degrees of heart disease and an additional 243 died. From this experience it can be assumed that of the 900 new patients each year, most of whom

are children, 400 may be expected to be left with heart disease, many permanently crippled, and over 200 may be expected to die within ten years.

Similar mortality statistics have been published from Philadelphia,[6] a community comparable to Boston in the incidence of rheumatic fever. During 1936, 357 deaths were reported as certainly

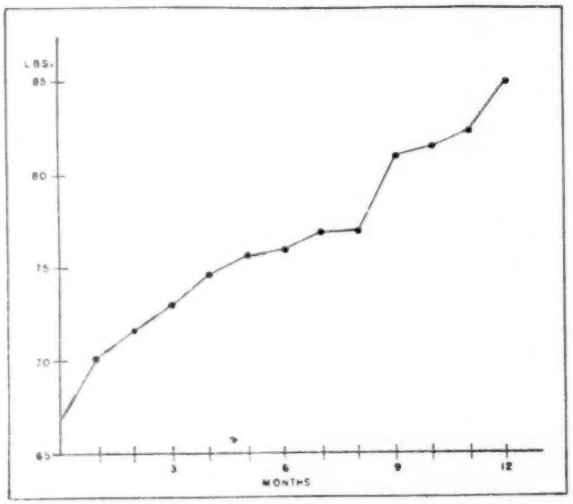

FIGURE 3.

Composite weight chart of the first 40 rheumatic children, showing the gain while at the sanatorium.

and 195 as probably due to rheumatic heart disease. Among persons under twenty years of age, rheumatic heart disease caused more deaths than did whooping cough, measles, meningococcal men-

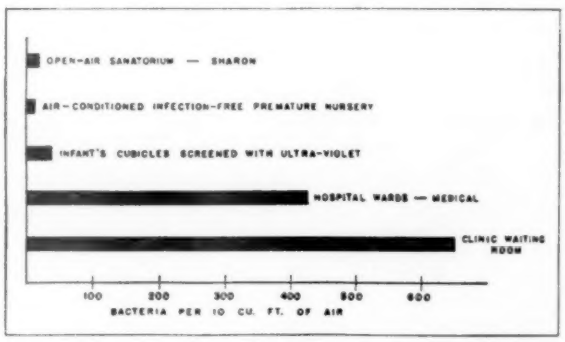

FIGURE 4.

Bacterial contamination of air at the sanatorium in comparison with an air-conditioned, infection-free nursery, infants' cubicles screened with ultra-violet light, hospital wards and waiting room (Fé del Mundo and McKhann[1]).

ingitis, diphtheria, scarlet fever and poliomyelitis combined.

There is reason to believe that carefully controlled, prolonged bed rest may have some bearing on the ultimate outcome for the individual case. At any rate, it is generally agreed that the rheumatic patient should be restricted to bed so long as there is any evidence of active infection, and should then have a further period of months of carefully regulated increasing activity. The duration of convalescent care is therefore comparable to that for tuberculosis. There are in Massachusetts over 4000 beds provided for patients with tuberculosis,[7] but only 177 for those with rheumatic fever.[3]

England has taken the lead in accepting the community responsibility for the care of rheumatic fever.[8] In London, it was recognized some years ago that the problem was too urgent and too extensive to be dealt with entirely by private or charitable organizations. The Ministry of Health therefore took active steps in the matter, the result being the provision of over 1000 beds for rheumatic children in the London area and an annual expenditure of over £220,000.

That the cause of rheumatic fever is still in doubt is a factor that has hampered progress in the care of patients. However, what we do know offers an approach to the problem. It is, for example, increasingly clear that there is a close relation between rheumatic fever and hemolytic streptococcal infections of the nose and throat.[9–11] Not only do such infections precede the initial attack of rheumatic fever, but they may also reactivate the infection during its convalescent stages. Every reappearance of the disease increases the likelihood of damage to the heart. Furthermore, when heart disease has already occurred, recurrences increase its severity and the chances of an early death. In Wilson's[12] series the mortality increased from 20 per cent when there had been only one attack to 64 per cent after four or more.

Prevention of colds and sore throats, therefore, becomes of the utmost importance for the rheumatic patient, and should be the criterion of any plan of hospitalization. This consideration has prompted transportation of these patients to a tropical climate where both respiratory diseases and rheumatic fever are less prevalent. Groups of children have been sent from Boston to Florida,[13] from New York to Puerto Rico[14] and from other places to Arizona.[15] The results have been disappointing. Some of the children sent to Florida[16] improved in the tropical environment, several had recurrences of rheumatic fever, and a few died. When the patients returned home they had little resistance to further infections. In other words, the tropical sojourn appeared to do no permanent good. Furthermore, from the economic point of view such a plan is impractical, since most of the rheumatic patients come from families with low incomes.

The method of caring for the children in small groups in an open-air sanatorium, although a rather different approach to the problem, has also been based primarily on an attempt to control respiratory infections within the group. In comparison with any transportation plan, it has the advantage of keeping the child in the sort of climate in which he will probably have to live, causing much less disruption of the family and being reasonable in cost. Furthermore, the child returns to his home in robust health, with increased resistance to the infections of his crowded home and school life. In short, the plan appears reasonable and has, during a preliminary period of two years, met with success.

Summary

During two years nearly 50 rheumatic children have been cared for in an open-air sanatorium, with excellent results. There was freedom from respiratory and recurrent rheumatic infection. The children showed a steady and uninterrupted gain in general health. These results are particularly encouraging in the light of the rather severe weather during the second winter and the accompanying prevalence of streptococcal infections and recurrent rheumatic fever in other hospital groups and elsewhere throughout the community.

Until further experience has been accumulated, it is unnecessary and unwise to attempt a close analysis of the various factors that may have contributed to the success of this enterprise. However, this type of treatment is rational and economically sound, and on the basis of experience to date deserves further trial.

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THE TREATMENT OF PEPTIC ULCER WITH ALUMINUM HYDROXIDE: A TWO-YEAR STUDY*

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THE treatment of peptic ulcer without complications is primarily medical. This principle is accepted today by an overwhelming majority of workers in this field. Such treatment, in addition to diet, rest and other usual hygienic measures, includes the reduction and, if possible, complete neutralization of hydrochloric acid in the stomach by means of various alkali substances. The second method has apparently not received the complete and wide approbation that has been accorded the first. We shall not present a detailed discussion of the importance or mere coincidental appearance of the acid factor in peptic ulcer. We have aligned ourselves, however, with those who believe that "one cannot discard the idea of acid and its effects on ulcer without coming to an impasse."[1] The unequivocal relation that acid bears to the problem of peptic ulcer rests on the foundations of experimental and clinical medicine. Experimental evidence, notably the work of Mann and Williamson,[2] Dragstedt[3] and others, has shown that the production of duodenal ulcers in dogs, the prevention of healing of these ulcers and their probable recurrence after healing are phenomena intimately associated with the unneutralized presence and unhampered activity of free acid in the stomach. Modern surgical endeavors are directed toward the removal of as large an acid-bearing area of the stomach as possible, and the consequent reduction of free acid to as low a level as possible. Lahey[4] expresses the trend of thought of many Continental and American surgeons when he says: "There seems little question that the best surgical results, immediate and remote, are in those ulcer patients who postoperatively have a very low gastric acid or gastric anacidity." Furthermore, Ivy[5] states that

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although "it cannot be proved that gastric juice is the factor initiating peptic ulcer, much evidence indicates that unneutralized gastric juice is an important if not a prime factor contributing to the chronicity of peptic ulcer."

Consequently, if we accept the principles that treatment of peptic ulcer is primarily medical and that such treatment should be substantially the inactivation of acid in the stomach, it perforce becomes a matter of distinct urgency to study and evaluate the effectiveness of the numerous neutralizing substances offered to the profession. Since the results for the first six months of the medical treatment of peptic ulcer are usually excellent, no matter what method is used, we decided to study the effectiveness of these antacids over a longer period.

This investigation, then, was undertaken with the express purpose of subjecting to a thorough study, covering a period of two years, the various antacids used in the Lahey Clinic for the reduction of gastric acidity in proved cases of peptic ulcer. We shall not concern ourselves with the subjective improvement of these patients, but shall confine our efforts to determining which of the various substances has been most effective over a two-year period.

Although this study deals primarily with the effects of various neutralizing agents, principally Sippy powders and aluminum hydroxide, as neutralizing agents after a prolonged period of use, it is of interest to note that clinically the results of treatment were approximately the same whichever of these two agents was employed. Whether some difference will develop after a longer follow-up period in the cases which still have a high acid level, principally those treated with Sippy powders, as against those which have shown a marked reduction in acid, principally those treated with aluminum hydroxide, remains to be determined. In a later paper we shall discuss the subjective and clinical improvement of patients under different types of medication over a long period of time. As a matter of fact, clinical results and subjective improvement depend so much on variables other than the type of medication used that it is difficult to evaluate the efficacy of any particular medication in the treatment of ulcer solely on this basis.

We reviewed the clinical records of 730 cases of peptic ulcer admitted between January, 1936, and January, 1938. This number constituted 3.4 per cent of the total admissions. There were 705 cases of duodenal ulcer, 14 of gastric ulcer, and 11 of jejunal ulcer. The sex ratio was 3 males to 1 female, in both duodenal and gastric ulcer cases. In the 11 jejunal ulcer cases, however, 10 patients were males. The youngest patient, seventeen years old, and the oldest, eighty-two, were both males. Two thirds of both males and females were between thirty and fifty-nine years of age.

For the purposes of this report we were able to utilize 308 cases. The others could not be included, because of insufficient data, incomplete study, questionable diagnosis or inadequate treatment.

Fourteen hundred gastric analyses were performed in the 308 cases, of which only 521 could be included in this report. Of these, 263 (50 per cent) were made following the use of Sippy powders exclusively, 159 (30 per cent) following the use of aluminum hydroxide exclusively, and the rest (20 per cent) following the use of mixtures and proprietary remedies.

It should be emphasized that these determinations of gastric acidity were done with an unvarying procedure throughout the study. Only those figures were used that were obtained after a standard Ewald test meal, given on a fasting stomach and aspirated forty-five minutes after the meal. No alkalies of any kind had been administered during the preceding twelve hours. Therefore, the figures obtained should indicate the functioning response of the gastric glands to the test meal without benefit of neutralizing agents. The determinations listed here are those of free hydrochloric acid, and are expressed as the number of cubic centimeters of N/10 sodium hydroxide required to neutralize 100 cc. of gastric juice.

The efficacy of Sippy powders in promptly neutralizing the stomach acidity when given in adequate doses is readily admitted. However, in the course of endeavors to neutralize completely the free hydrochloric acid, symptoms of toxemia and alkalosis develop in a considerable number of patients. It has also been observed that patients with ulcer and renal insufficiency, hepatic cirrhosis, arteriosclerosis or hypertension are markedly susceptible to alkalosis. Furthermore, an objectionable feature of the sodium bicarbonate in the Sippy powders has been the tendency for the acid content to return to higher levels following their use. Consequently, many neutralizing substances have been offered that allegedly provide adequate neutralization without the associated ill effects of toxemia and alkalosis. One of these that has received wide use and approval is aluminum hydroxide. Original papers by Crohn,[6] Rowland and his associates[7, 8] and Jones[9] have expressed favorable opinions of the value of this substance. It is claimed that it combines with hydrochloric acid to form aluminum chloride and that no matter how much is given, an alkaline reaction cannot be produced,

because of its amphoteric qualities. In the small intestine, the biliary and pancreatic secretions react with it to re-form sodium chloride and re-precipitate aluminum hydroxide. It is therefore claimed that colloidal aluminum hydroxide can act as an efficient neutralizer of gastric acidity, is nonabsorbable and is thus incapable of producing alkalosis.

Acid determinations were made at periods of three, six, nine, twelve and twenty-four months in order to ascertain what changes, if any, occurred at these times as compared with the gastric analysis made on the first admission. An increase in acidity was taken to mean one of 20 units or over; a decrease to mean one of 20 units or over, and little or no change to mean an alteration of not more than 19 units in either direction.

As shown in Table 1, at the end of three and six months following the use of aluminum hydroxide there was a decrease in gastric acidity in 42

TABLE 1. *Deviations from Original Acid Level in 308 Cases.*

No. of Months of Treatment	Decrease		No Change		Increase	
	Sippy powders	Aluminum hydroxide	Sippy powders	Aluminum hydroxide	Sippy powders	Aluminum hydroxide
	%	%	%	%	%	%
3	27	42	58	48	14	10
6	19	45	74	40	7	15
9	20	42	65	47	15	11
12	25	52	59	44	16	4

and 45 per cent of the determinations, respectively, whereas following the use of Sippy powders there was a decrease in only 27 and 19 per cent, respectively. At the end of nine and twelve months following the use of aluminum hydroxide there was a decrease in acid in 42 and 52 per cent, respectively, of the determinations, whereas following the use of Sippy powders there was a decrease in only 20 and 25 per cent, respectively.

Thus, throughout the first year, aluminum hydroxide produced a decrease in gastric acidity in over 40 per cent of determinations, and was apparently twice as effective as Sippy powders in reducing acidity. Also, a slightly smaller percentage of aluminum hydroxide determinations showed an increase in gastric acidity at each of these monthly periods, except at the end of the six-month period.

Another development noted was the effectiveness of aluminum hydroxide in reducing gastric acidity as much as 40 and 50 units from the original acid level. Following the use of Sippy powders, only 8 acid determinations were reduced 40 units, and none 50 units. Following the use of aluminum hydroxide, however, 30 determinations showed the acidity as reduced 40 and 50 units. These findings are interesting because there were more determinations following the use of Sippy powders than following aluminum hydroxide therapy. Certainly, the effectiveness of aluminum hydroxide in controlling acidity even over a long period of time is well demonstrated (Table 2).

To test the effectiveness of these neutralizers still further, it was decided to study 63 cases in which complications were present. In these cases

TABLE 2. *Cases Exhibiting a Maximum Decrease in Gastric Acidity.*

No. of Months of Treatment	40-Unit Decrease		50-Unit Decrease	
	Sippy powders	Aluminum hydroxide	Sippy powders	Aluminum hydroxide
3	1	6	0	5
6	0	1	0	2
9	0	3	0	2
12	0	2	0	3
24	0	0	0	1

medical treatment had admittedly been unsatisfactory, and there was an urgent necessity to reduce gastric acidity as much as possible, to provide healing of tissue and prevent chronicity and further inroads of the disease.

There was a history of recent hemorrhage in 21 cases; obstruction was present in 14; 7 patients had had a gastroenterostomy, 4 of whom had gastrojejunal ulcer on admission. The 21 remaining cases had various other complications among which may be listed 5 cases each with diaphragmatic hernia and with duodenal diverticula, 2 with gallstones, 2 with associate gastric ulcers, 1 with perforation, 2 with thyroid disease and 3 with renal stones.

From the records, we were able to list 82 acid determinations following the use of Sippy powders and 38 following that of aluminum hydroxide. The latter produced a decrease of 20 units or over in gastric acidity in 48 per cent of all determinations, whereas the former resulted in a decrease in only 17 per cent. This is additional evidence to show that even in ulcer cases with complications, in which neutralization is so important, aluminum hydroxide seems to be twice as effective in reducing gastric acidity as are Sippy powders.

Remembering that the longer the duration of symptoms in these ulcer cases, the less favorable becomes their response to medical treatment, we thought that a study of those cases in which the duration of symptoms was over twenty years would prove enlightening. There were 30 such cases in the series, of which only 12 could be used for the purposes of study. There were complications in half these cases, the average age was fifty-eight and the average duration of symptoms was thirty years, all these factors being definitely unfavorable

so far as response to medical therapy and neutralizers is concerned. In the 23 acid determinations, 6 of the 7 cases receiving aluminum hydroxide showed a decrease of 20 units or more, whereas only 2 of the 5 receiving Sippy powders showed such a decrease.

Conclusions

The neutralization of gastric acidity is an integral part of the medical treatment of peptic ulcer.

The results of a two-year study covering the comparative neutralizing effectiveness of two antacid substances, Sippy powders and aluminum hydroxide, in reducing gastric acidity are presented.

Following the use of aluminum hydroxide, 40 per cent of the acid determinations at the end of three, six, nine and twelve months showed a reduction in gastric acidity of 20 units or over. Following the use of Sippy powders, only approximately 20 per cent of the determinations showed such a decrease.

There were more than three times as many reductions of 40 and 50 units and over following the use of aluminum hydroxide than there were following the use of Sippy powders.

In the cases with severe complications and in those with a duration of twenty years and over, aluminum hydroxide also showed greater effectiveness in reducing acidity than did Sippy powders.

Summary

In a study of 308 cases of peptic ulcer, reviewing 521 gastric analyses, it was found that aluminum hydroxide is a much more effective neutralizer over a long-term period than are Sippy powders.

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THE REACTION OF LEUKEMIC PATIENTS TO SULFAPYRIDINE ADMINISTRATION*

A Preliminary Report

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BOSTON

NUMEROUS reports[1–6] in the recent literature refer to the leukopenia due to sulfapyridine and related drugs, but we know of no study reporting their effects on patients with leukemia. This paper concerns observations on the reaction of 9 such patients to the administration of sulfapyridine. The first observations were made on a patient (Case 1) who had received routine x-ray therapy. A few days later he developed lobar pneumonia and was given sulfapyridine. The changes in the white-cell count during this period led to the investigation.

Case 1. W. B. (H. M. H. 39-1003), a 70-year-old man, entered the hospital on August 7, 1939, with symptoms of 1 year's duration that were typical of chronic lymphatic leukemia. The white-cell count was 256,000, with 90 per cent lymphocytes and 8 per cent lymphoblasts. The patient received 1000 r (1000 kv.) of x-ray therapy. The white-cell count was falling 4 days after the last x-ray treatment, when the patient developed lobar pneumonia (Type 14). He was given sulfapyridine in routine dosage. The drug was discontinued after 48 hours because the white-cell count had reached 7100. The pneumonic process did not clear, although the patient was afebrile for 4 days. On the 5th day he had a sudden chill, with clinical evidence of active pneumonia in the same area. The patient was again given sulfapyridine, but in restricted dosage. During the following 4 days the white-cell count fell from 10,850 to 6500, and then rose slowly after the drug was withdrawn. Because of the possibility that the sulfapyridine might bear some specific relation to the fall in the white-cell count, it was decided to study the patient's reaction to the drug in the absence of infection.

After 17 days the white-cell count had risen to 33,500. The patient received 5 gm. of sulfapyridine by mouth in a period of 12 hours. During the following 32 hours the white-cell count fell to 11,000. The patient was discharged to the Outpatient Department.

Twenty-one days later the patient's reaction to the drug was again studied. The white-cell count had risen to 47,000. The response to sulfapyridine is shown in Figure 1.

The patient was followed in the Outpatient Department for the next 2 months, during which the white-cell count

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rose to 94,000. He was readmitted to the hospital and again given sulfapyridine. The response is shown in Figure 2. Six days after admission the patient was given a single intravenous dose of 5 gm. of the soluble sodium salt of sulfapyridine. At this time the lymph nodes were palpable but not grossly enlarged. Four hours after receiving this dose the patient complained of soreness in the region of the cervical and axillary lymph nodes. This increased during the night and required medication to control pain. Within 18 hours after sulfapyridine had been given, lymph nodes throughout the body were grossly enlarged, very tense, warm and tender to palpation. Forty hours after injection two cervical nodes were removed for study. One of these showed a large central focus of hemorrhage. A wet smear of the node before fixation

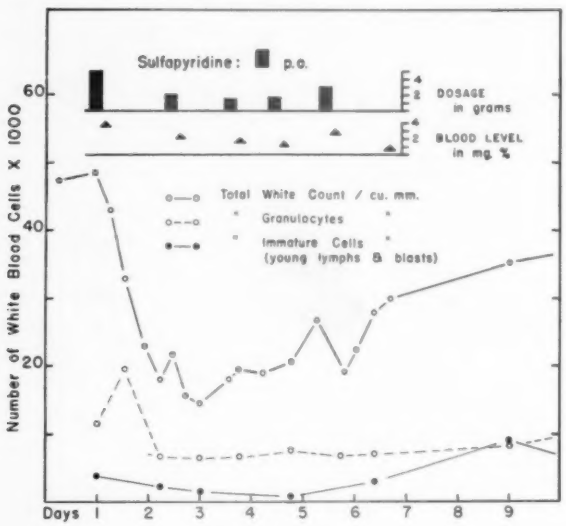

FIGURE 1. *Case 1.*

showed cells identical with the blast forms which had appeared in the peripheral blood smear within a few hours after the drug had been given by vein. Lymphoblasts, which had previously been rare in the circulating blood (0.0 to 2.0 per cent), rose to 10 to 14 per cent. It was believed that the drug in high concentration had produced cell destruction, particularly in the lymph nodes, and that the products of cell breakdown had led to an acute local inflammatory reaction. The patient was discharged to be followed in the Outpatient Department. At the time of discharge the white-cell count was rising. The enlarged nodes were obviously beginning to regress. It was not possible to determine accurately whether the spleen had shown a parallel fluctuation in size. The nodes returned to their former size in a period of 8 to 10 days.

CASE 2. J. H. (H. M. H. 39-1239), a 15-year-old schoolboy, was first admitted to the Massachusetts General Hospital because of dyspnea of 12 days' duration. X-ray examination showed a large tumor mass in the mediastinum. Examination of a biopsied supraclavicular lymph node showed malignant lymphoma of the lymphoblastic type. The patient received 1300 r (200 kv.) of x-ray therapy to the chest. At the time of discharge the mediastinal shadow was considerably reduced and the patient's symptoms alleviated.

Five weeks after the patient's first symptoms, he was seen at this hospital. Examination of the blood showed a white-cell count of 15,200, with 52 per cent polymorphonuclears, 10 per cent band forms, 19 per cent lymphocytes, 12 per cent monocytes, 1 per cent metamyelocytes, 3 per cent eosinophils and 2 per cent basophils. The platelets appeared to be reduced.

Two months after the onset of symptoms the patient was admitted to the hospital in a critical condition, with the picture of acute lymphatic leukemia. There was marked anemia, bleeding, slight lymph-node enlargement and a palpable spleen. The blood study showed a red-cell count of 2,530,000, with 55 per cent hemoglobin (Sahli). There was a white-cell count of 212,000, with 1.5 per cent polymorphonuclears, 0.5 per cent basophils, 1.5 per cent small lymphocytes, 3.0 per cent medium lymphocytes, 88.5 per cent atypical lymphocytes and 3.0 per cent blasts. The platelets appeared to be reduced. The patient was immediately given a transfusion of 350 cc., following which the white-cell count was 183,750. He was given sulfapyri-

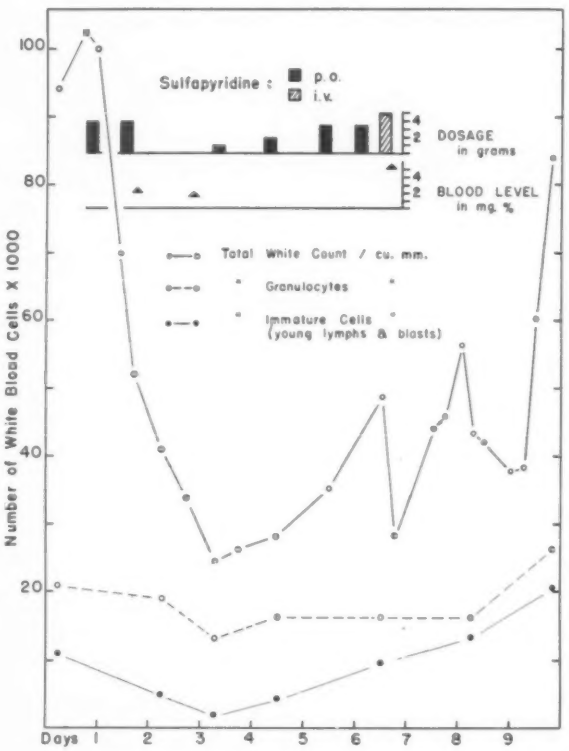
Sulfapyridine: p.o. i.v.
DOSAGE in grams
BLOOD LEVEL in mg. %
Total White Count / cu. mm.
Granulocytes
Immature Cells (young lymphs & blasts)
Number of White Blood Cells X 1000
Days

FIGURE 2. *Case 1.*

dine. Changes in the white-cell count, the dosage, the blood level of the drug and the transfusions are indicated in Figure 3. In addition to the marked change in total white-cell count, there was a distinct change toward maturity in the character of the cells. On the 19th day of treatment the drug was discontinued, because in spite of the change in blood picture there was clinical evidence of widespread leukemic infiltration.

CASE 3. E. F. (H. M. H. 35-481), a 60-year-old woman, was found on routine examination to have an asymptomatic chronic lymphatic leukemia, with a white-cell count of 59,000, with 85 per cent lymphocytes. This diagnosis was confirmed by examination of a biopsied supraclavicular lymph node. The patient required no treatment for the disease, since her general health was excellent. She was given a small dose of sulfapyridine by vein to determine

whether the drug would produce changes in the white-cell count similar to those seen in Cases 1 and 2. In the 18 hours after she had received intravenously 2.5 gm. of the soluble sodium sulfapyridine, the white-cell count fell to 29,000. Equal doses at 24 and 48 hours produced no further significant fall in the count. The patient was discharged with a white-cell count of 26,100.

In addition, 6 other cases of leukemia have been studied. Case 4 (H. M. H. 39-1429) and Case 5 (H. M. H. 39-1341) were those of patients with chronic lymphatic leukemia. Both were given adequate doses of the drug, orally and intravenously, to attain high blood levels. Neither case showed

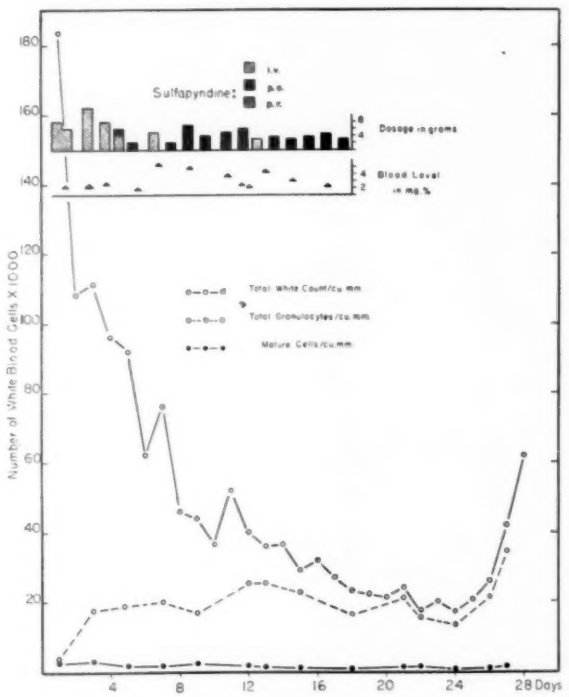

FIGURE 3. *Case 2.*

a definite response. Examination of biopsied lymph nodes before and after treatment in Case 4 showed no significant microscopic change, although grossly there was obvious edema.

CASE 6.* H. L. (P. B. B. H. 114080) was a 57-year-old patient with chronic lymphatic leukemia, whose reaction to the drug was observed during treatment for lobar pneumonia. The white-cell count on admission was 70,000. He was given sulfapyridine orally, and the blood level reached 10.4 mg. per 100 cc. In 3 days the blood count had fallen to 22,400. The patient was discharged without treatment for leukemia, but returned 2 months later, again with lobar pneumonia. The white-cell count, which was 74,000 at the time he received sulfapyridine, was 49,000 10 days later. This was not a clear-cut response. Both changes in the white-cell count may have been due to coincidental infection.

The effect of sulfapyridine was studied in Case 7 (H. M. H. 39-1083), Case 8 (H. M. H. 36-915) and Case 9 (P. B. B. H. 112506), all of which were cases of chronic myelogenous leukemia. Cases 7 and 8 were followed closely during the periods in which they received sulfapyridine, but there was no change in total or differential white-cell count that could be attributed to the drug. In Case 9, the patient was admitted with lobar pneumonia, and was given the drug orally in adequate dosage. No significant change was observed either in total or differential white-cell count.

Sulfapyridine produced palpable changes in the lymph nodes of all the cases of lymphatic leukemia. The extent of this reaction varied with the dosage of the drug; it consisted of swelling, noticeable within twelve to eighteen hours after the drug had been given, followed by a slow decrease in size to less than that prior to treatment. The most marked reaction of this type followed intravenous administration of the drug in Case 1. It is possible that the effect of x-ray therapy might be considerably increased if it were given during the period of local reaction in the nodes.

We have presented these cases as a preliminary report. It is suggested that further investigation may identify related compounds more effective than sulfapyridine in producing this type of reaction. Experimental studies directed to this phase of the problem are being carried out.

SUMMARY AND CONCLUSIONS

Three of 6 cases of lymphatic leukemia showed a rapid fall in lymphocytes when sulfapyridine was given. A fourth case showed a similar but not conclusive response. This reaction to the drug is apparent within twelve to eighteen hours after its administration, and appears even when its blood level is low. It is a transitory effect. In none of the cases was the fall in total white-cell count attributable to granulocytopenia.

In 3 cases of chronic myelogenous leukemia, no comparable response to sulfapyridine occurred.

These observations are interesting because recent reports on the effects of sulfapyridine on the hematopoietic system emphasize granulocytopenia. The reactions reported here appear to be different, and suggest a specific effect on the leukemic lymphocytic cell.

*Cases 6 and 9 are reported through the courtesy of the Medical Clinic, Peter Bent Brigham Hospital, Boston.

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THE USE OF OXYGEN IN DEMONSTRATING POSTERIOR HERNIATION OF INTERVERTEBRAL DISKS*

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IT HAS been established beyond a doubt that posterior herniations of intervertebral disks form another important link in the chain of etiologic factors that may cause low-back and sciatic pain, and that they form one of the most favorable conditions in the lumbosacral spine for surgical treatment. In the past this condition went unverified many times even though perhaps suspected, because the surgeon hesitated to introduce Lipiodol into the subarachnoid space unless there was reasonable assurance that herniation was present so that the oil could be removed at the subsequent laminectomy.

The true nature of these pseudotumors has been recognized for many years, and they were at times referred to as enchondromas. Dandy[1] was one of the first to describe and designate the condition properly. To Mixter and Ayer,[2] Mixter and Barr,[3] and Hampton and Robinson,[4] however, belongs the credit for emphasizing the importance of recognizing the posterior protrusion of the degenerated portions of intervertebral disks in the lumbosacral region, as well as for verifying the presence of such a protrusion by the use of Lipiodol and the fluoroscope. As soon as their work had been published, neurosurgeons as well as bone and joint surgeons suspected that many patients who had responded poorly to measures used to relieve sciatic pain probably had posterior herniations of intervertebral disks. This proved to be true in many cases, and because of this, perhaps, the actual percentage of patients who had herniations as a cause of low-back pain with sciatic radiation was somewhat distorted, and for a time Lipiodol was used oftener than was necessary. Nevertheless it has been shown in many sections of this country that posterior herniations of intervertebral disks do play a dramatic role in the large group of etiologic factors capable of producing sciatica, a reasonable estimate being probably 2 to 3 per cent. The only figures that are available at present are those of the Mayo Clinic as given in the apparently astounding number of well over 500 verified herniations that have been successfully operated on; in reality these represent only 1.8 per cent of all patients they see with low-back pain. In the Lahey Clinic the percentage has been 3 since the first patient with herniated disk was operated on in 1936.

Until recently Lipiodol has been the agent usually employed in verifying the presence of herniated disks. A few untoward effects were noted. This naturally created an interest in developing a technic that would visualize the presence of herniated disks by a medium that would be less irritating and at the same time would quickly be dissipated from the subarachnoid space. Lipiodol does not disappear from the subarachnoid space for many years and may stay indefinitely. Periodic fluoroscopic examinations have demonstrated that it usually moves freely in the space and that only in a few cases does it become encysted. In cases in which the latter occurs or in which the subjective symptoms become more marked following the injection of Lipiodol, the oil is certain to receive the blame for the entire symptomatology. It must be remembered that an intraspinal lesion was present before oil was injected, and that the pain may therefore be only a part of the original picture. It is logical to assume, however, that if an active, acute or chronic inflammatory change is present in the form of arachnoiditis or radiculitis, any irritating substance that remains in the spinal canal for years may produce denser adhesions, and Nature may attempt to wall off the foreign material and create a cystic arachnoiditis. For that reason, if an inflammatory condition is suspected, the use of Lipiodol should be avoided.

At the present time oxygen is used exclusively at the Lahey Clinic to demonstrate defects in the lumbosacral canal, and we consider it to be as efficient as Lipiodol in the visualization of posterior herniations of intervertebral disks. This statement would have been considered entirely too enthusiastic in our early experience with air, since the technic and lack of ability to interpret the spinogram failed to demonstrate accurately the presence of an intraspinal defect. However, by the continued co-operation of the radiologists, the importance of which cannot be overemphasized, a satisfactory routine has been instituted.

Following the pioneer work of Dandy, to whom, of course, belongs the credit for using air to visualize the intracranial and intraspinal fluid spaces, Coggeshall and von Storch,[5] in Boston, and

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Scott, Young and Chamberlain,[6–8] in Philadelphia, were among the first to publish reports on the use of air in myelography.

It is true that the Lipiodol method is considerably easier for both the surgeon and the radiologist, since it takes only a relatively short time to

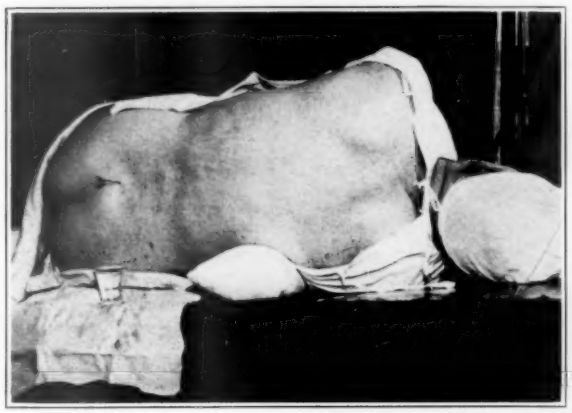

FIGURE 1.

The patient is placed on the x-ray table with the side up in which the pain is severest. The head is elevated while 40 cc. of fluid is allowed to escape from the spinal canal.

complete the introduction of Lipiodol and the fluoroscopy. Fluoroscopic examination is of no value in oxygen spinograms with the present x-ray equipment. The use of oxygen is much more

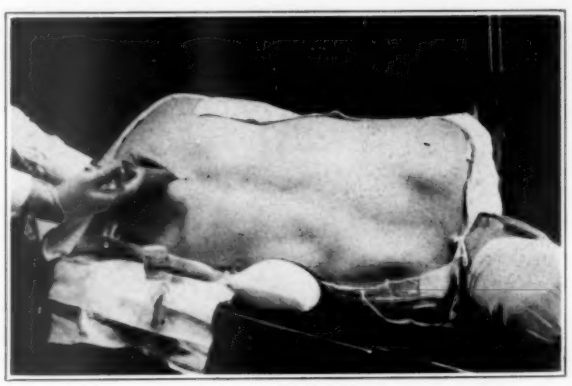

FIGURE 2.

The table is then tilted to the Trendelenburg position, 30° angle, and the escaped fluid is replaced by 50 cc. of oxygen.

time-consuming, since it is imperative that an accurate filling of the lower canal be made and that the wet films be examined before the patient is removed from the x-ray table. This, of course, is when most of the time is lost. If the roentgenograms are satisfactory, that is, if they demonstrate the deformity or show an entirely normal canal, nothing further has to be done. On the other hand, at times there may be a suspicious defect, although not conclusive, and it is then necessary to take small spot stereoscopic films of the region in question.

The technic that is now used is as follows. The patients chosen for this procedure are those who have low-back pain with or without sciatic radiation, in whom roentgenograms of the spine and sacroiliac regions do not show adequate cause for

FIGURE 3.

A sloping defect is demonstrated which separates the posterior longitudinal ligament from the superior margin of the fourth lumbar vertebra to the inferior margin of the fifth.

their discomfort and who have had sufficient investigation, including a neurologic examination and the elimination of foci of infection. The patient is given a large amount of premedication, usually including morphine and some form of barbiturate. He is then placed on a tilting table with head and shoulders higher than the rest of the body, in other words, Fowler's position, on the side opposite the pain. A spinal needle is inserted into the subarachnoid space between the fifth lumbar and first sacral spinous processes (Fig. 1). Studies of the dynamics are carefully performed, and the first 2 or 3 cc. of fluid is kept separate for determination of the total protein, after which 40 cc. of fluid is allowed to escape or is aspirated with the syringe. The patient may complain slightly of a headache on withdrawal of the fluid.

He is then tilted downward to a 30° angle (Fig. 2). A 50-cc. syringe filled with oxygen is attached to the needle, and the entire amount injected at one time, although not too rapidly. The patient usually says that the hip on the upper side feels numb immediately after the oxygen is introduced. A simple way of obtaining the oxygen is by attaching a sterile rubber tube to the oxygen outlet and allowing the oxygen to flow through this into the closed syringe. The pressure of the oxygen will slowly dislodge the piston until the

FIGURE 4.

This shows a sharply demarcated posterior protrusion, with the posterior longitudinal ligament separated only opposite the intervertebral space.

amount desired has entered the syringe. The needle is withdrawn with the syringe still attached. Lateral roentgenograms may be taken at this time, thus avoiding too much turning of the patient. The patient is then placed on his back, and the anteroposterior exposures are made.

It was at first thought necessary to take many oblique views to demonstrate defects in the oxygen column. However, we have found them of little value. In our experience, the stereoscopic anteroposterior and lateral views, if proper filling has taken place, demonstrate any defect that could be seen by other views. If the patient is allowed to remain in the Trendelenburg position for twelve to eighteen hours, little discomfort or headache will be noted.

Because of the lack of density, oxygen spinograms do not lend themselves to reproduction so well as Lipiodol spinograms. Nevertheless, with the stereoscopic view and proper interpretation, oxygen spinography is satisfactory and far superior in cases in which some question exists as to whether Lipiodol should be introduced. Such patients can have spinograms with oxygen taken without fear of untoward result.

Oxygen spinograms were made in 175 patients suspected of having herniated intervertebral disks. Of these, 150 were proved to have herniated disks by operation. In 5 of the latter it was necessary to inject Lipiodol as well as oxygen before the diagnosis could be made, this being due to faulty technic or to improper interpretation of the films at the time when we were inexperienced in the

FIGURE 5.

This represents a normal lumbosacral subarachnoid space filled with oxygen.

use of oxygen. In 25 cases the spinograms were interpreted to be negative, and for that reason the patients were not subjected to operation. How many of these will prove to have a herniated intervertebral disk at a later date is of course not known. It is only fair to say that the percentage of oxygen spinograms that were negative for herniation may be greater than that with Lipiodol, since no hesitancy is exercised in using oxygen in

patients whose histories and findings are not entirely typical of the condition. Lipiodol is still used if the herniation is suspected at a level higher than that of the twelfth thoracic vertebra, provided that subarachnoid block is not present; if a block is demonstrated, oxygen is used. It is conceivable that filling the entire spinal canal by the cisternal route, such as is done by a few neurosurgeons, may demonstrate the cervical, thoracic and upper lumbar canal satisfactorily. Interpretation of the spinograms is not difficult in most cases, but it may be exceedingly so. It behooves the roentgenologist and neurosurgeon to study the films stereoscopically, and when oxygen is used decision must often be reserved until the roentgenograms have thoroughly dried so as to avoid the possibility of overlooking a small lateral defect.

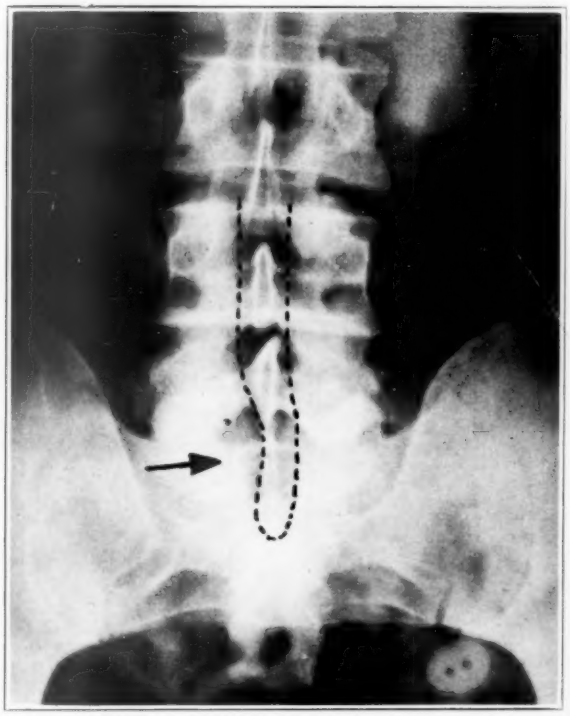

FIGURE 6.
In this film there is a sharply localized defect.

In the interpretation of the spinograms, considerable difficulty is first experienced in disregarding the many overlying outlines of bone. This is true to a lesser extent in the lateral stereoscopic views than in the anteroposterior views. Since the great majority of defects are found between the fourth and fifth lumbar and the fifth lumbar and first sacral vertebrae, considerable time should be taken in studying this region. The small lateral defects can usually be demonstrated in the anteroposterior view by lack of filling of the subarachnoid space around the nerve root, with only a very slight defect in the main air column. The lateral views are of no great value in demonstrating this type of lesion, since it may be completely covered with a layer of oxygen.

A posterior defect may often be seen in the air column, with an associated lipping of the posterior edges of the bodies of the vertebrae. However, the roentgenograms which show posterior lipping of all the lumbar vertebrae, with slight protrusions causing defects in the air column, certainly must not be considered similar to the single ones, since the subarachnoid space around the nerve roots can be seen to fill normally in the former. These cases should be classified as posterior protrusions of intervertebral disks rather than as herniation or rupture. Laminectomy is not considered in this type.

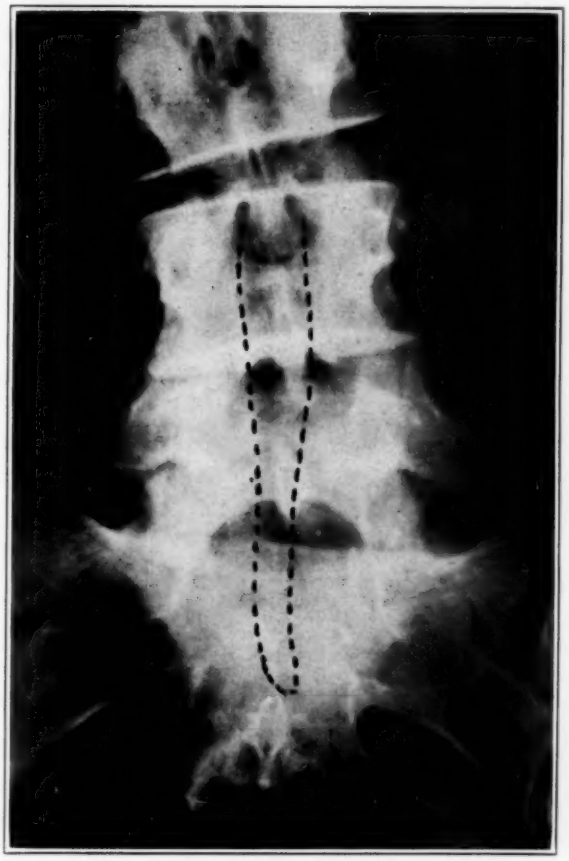

FIGURE 7.
This demonstrates a sloping lateral defect pushing the canal to one side rather than indenting it, as shown in Figure 6.

There is, of course, considerable variation in the type of defect in the air column in different patients. The lateral view may show no defect, especially if the protrusion is small and laterally

placed, whereas it may show the longitudinal ligament separating from the immediate posterior surface of the fourth body near its upper end to the inferior margin of the fifth body below, causing a sloping protrusion (Fig. 3) or an acute defect sharply limited to the interspace (Fig. 4). Columns of oxygen do not lend themselves well to reproduction, and for that reason the anteroposterior views, when not seen stereoscopically, show only a faint outline (Fig. 5), which is a normal dural lumbosacral canal; however, a rather sharp defect may be seen in the lateral portion of the dural canal at the lumbosacral junction (Fig. 6). At times one can demonstrate a defect that seemingly displaces the dural canal away from the lesion rather than indenting it (Fig. 7).

Summary

Oxygen spinograms on 175 patients suspected of having herniated intervertebral disks were thought to be positive, and later verified by operation, in 150. In 5 of these, Lipiodol was injected because the oxygen spinograms were found to be unsatisfactory because of faulty technic or of improper interpretation at the time when we were inexperienced in the use of oxygen. In 25 cases the spinograms were interpreted to be negative, and the patients were not subjected to operation.

The advantages of oxygen over Lipiodol are obvious. The disadvantages are: there is increased temporary discomfort for the patient; re-examination is impossible at a later date unless the entire procedure is repeated; as a contrast medium, oxygen is relatively poor.

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REPORT ON MEDICAL PROGRESS

FIRST-AID TREATMENT FOR ASPHYXIA

Charles C. Lund, M.D.*

BOSTON

BECAUSE a physician is seldom present when asphyxial accidents occur, the contributions of the medical profession in this field are usually carried to the victims of accidents through an intermediary, a layman trained in first aid. Here the responsibility of the profession to the public is similar to that in connection with nursing technic — that is, a responsibility for research, education and standards of performance. Any new developments in knowledge or technic must be very carefully considered and tested because of the tremendous task of re-education involved. For the benefits of any new scientific discoveries used directly by the profession to be of value to the public, the education of the profession, and the education of the public to accept or demand the new services from the profession are essential. In first aid, however, there are three steps: education of the profession, education by the profession of first-aid men to understand and accept the methods, and education of the public to accept or demand the new technics. Without enthusiastic promotion by physicians, progress in first aid is apt to be slow. Improvements in the technic of first aid for asphyxia have not been marked in the last ten years, but the diffusion to trained first-aid men of the knowledge of the gains of the previous twenty years has progressed very rapidly; consequently a large body of intelligent men in all walks of life now know what to do in cases of drowning and other types of asphyxia. Many of these have made a profession of first aid and rescue work, and are to be found largely among rescue crews of gas companies, attendants at public bathing beaches and teachers of first aid employed by such organizations as the American Red Cross. Because all members of the medical profession have not become familiar with the modern methods taught these men and have not had the practical experience in handling victims of drown-

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ing and asphyxia, embarrassing situations occasionally arise. Above all, physicians must be very careful not to pronounce death prematurely in victims receiving artificial respiration, since nothing can hurt the profession more than to have a layman save a victim after a doctor has pronounced him dead — this has actually happened.

Victims of drowning or other types of asphyxia who show any sign of life must have immediate aid to survive. Place the victim in the prone position suitable for artificial respiration and then *give it*. No time must be wasted finding the best possible place; whatever reasonably good place can be reached in a few seconds must be used. The head must be turned to one side and must rest on the victim's hand; this keeps the mouth out of water or sand. If possible the body must lie head *downward* on a 20 or 30° slope, so that any fluid may easily run out of the bronchi and trachea. Then the prone-pressure (Schäfer) method of artificial respiration must be used. This procedure has displaced all other methods, for good physiological reasons,[1] except in the later stages of pregnancy or after an abdominal operation, when the Sylvester method is better.[2] The technic is described in all modern first-aid manuals published in the United States and Great Britain.[3] In addition to artificial respiration, every effort, short of stopping the attempt at resuscitation, must be made to keep the victim warm. Stimulants are of no use, and most of them are harmful — except, possibly, caffeine given in moderate dosage intravenously.

An advance in technic for certain cases was recently published by Drinker[4] and by the Consolidated Edison Company of New York.[5] This new technic, called "pole-top resuscitation," was devised to reduce one type of preventable death, namely, that of the shocked linesman who receives artificial respiration too late because of the difficulty of getting him to the ground. The paper and the booklet give detailed instructions how to approach the unconscious man who is hanging by his safety belt and how to put him in proper position for artificial respiration astride the rescuer's safety belt. Then come the following instructions that are of interest to any student of artificial respiration because they show the necessity of adapting technic to special conditions in exceptional circumstances.

> He shall then push the victim's head forward and apply pole-top resuscitation by following these steps:
>
> Encircling the man's waistline with his arms, placing one open hand on the abdomen and grasping the first hand with the fingers of the other to insure a firm grip.
>
> Applying pressure upon the man's abdomen, in an inward and upward direction, then completely release pressure, to a time rhythm similar to that of normal breathing, which is approximately about four seconds a stroke.

The booklet contains a chart that shows the importance of speed in all rescue work so that artificial respiration may have a chance of success (Fig. 1). This chart is equally applicable to drowning accidents. It should be remembered that the person who is removed from water and is not breathing continues to drown until artificial respiration starts. In all steps up to this, immediate and prompt action is absolutely essential. People have died after ceasing to breathe for two minutes, in spite of subsequent, continuous and presumably adequate artificial respiration. Conversely, nobody can live whose lungs have had no change of air for over twelve minutes.

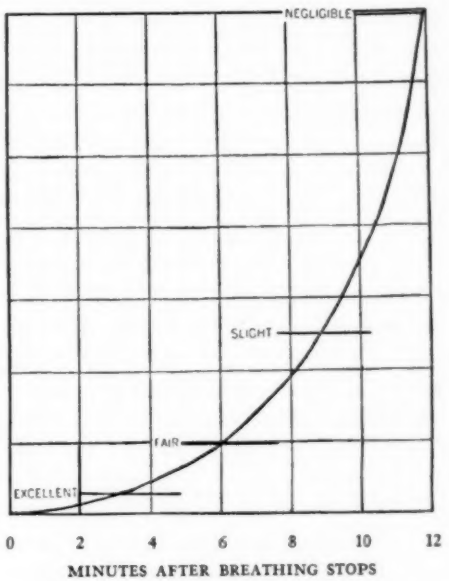

FIGURE 1. *Cessation of Breathing and Resuscitation. (Reproduced from* Pole Top Resuscitation[5] *by permission of the publisher.)*

It is assumed that a healthy adult stops breathing at 0. The chances of restoring respiration by appropriate measures are indicated by the curve.

Granted that the victim has a chance of survival at the start of artificial respiration, the procedure must be kept going for at least two hours unless good spontaneous respiration or positive signs of death have supervened.

INHALATORS

When asphyxia results from electric shock, drowning in water or solids, inhalation of a solid body, or breathing air of low oxygen content, — in sewers and under certain conditions in mines,

—the problem is to get oxygen into the lungs. This can be done with artificial respiration in normal air about as rapidly as with any special oxygen mixture, even if the oxygen is immediately available. Asphyxiation with carbon monoxide is a different problem. A full consideration of all aspects of this problem will be found in the recent book by Drinker.[6] With this type of asphyxia, artificial respiration with oxygen, as first suggested by Bernard[7] in 1857, is better than artificial respiration with air. Better still is the administration of a mixture of oxygen and carbon dioxide, which was first recommended by Henderson and Haggard.[8] Originally they suggested a mixture containing 90 per cent oxygen and 10 per cent carbon dioxide, but in 1922 they[9] reduced the carbon dioxide content to 5 per cent for field use. Further experience showed that this mixture did not produce the optimum stimulation of respiration, and in 1929, following a study by Heller, Killiches and Drinker,[10] a shift to 93 per cent oxygen and 7 per cent carbon dioxide was suggested. Following this, emergency crews using the new mixture reported a prompt decrease in the percentage of deaths in treated cases. This mixture has been standard ever since.

This gas mixture is given through a respirator held over the face by one man while another gives artificial respiration. It is important to keep administering the gas for one to two hours after spontaneous respiration has been established, and to be ready to readminister it at any time within the next twenty-four hours if normal respiration should become too shallow.

Several inhalators are on the market, and a few—the H–H, the B–K and the Davis—have been accepted by the Council on Physical Therapy of the American Medical Association. In principle they are like an old type of apparatus to give nitrous oxide anesthesia, being arranged to prevent rebreathing. It must be remembered, however, that in asphyxia due to carbon monoxide as well as in other types immediate artificial respiration is essential, and that there must be no delay while waiting for apparatus.

The Use of Respiration Apparatus

The idea of blowing air into the lungs and sucking it out again has always appealed to the inventive genius of the human race. Keith[11] gives a history of such devices up to 1909. Any contrivance that is to be successful in giving "suck-and-blow" artificial respiration must be safe and effective. One of the dangers is that of causing pulmonary collapse and atelectasis. The lungs will stand very little pressure applied through the trachea. Any machine that blows in gas can potentially inflate the lungs to the bursting point with release of less than a thousandth part of the original pressure in the gas tank. Proper mechanical devices can probably eliminate most of this danger, but to date no such machine has eliminated all danger and at the same time provided a type of artificial respiration so safe, sure and foolproof as that applied manually by trained men. The old Pulmotor was so harmful that even in spite of the sale of thousands the company producing it failed and went out of business after a report by the Commission on Resuscitation from Carbon Monoxide Asphyxia[12] in 1923. Recently another "resuscitator" has come on the market and has been accepted by the Council on Physical Therapy of the American Medical Association.[13] This one, the E and J Inhalator and Resuscitator, was accepted over the strenuous protest of Henderson[14] who believes that the resuscitation part of this machine is just as dangerous as the Pulmotor, because mechanically it is very similar. He protested because he was afraid of two results from the use of the machine: first, that people would delay artificial respiration while waiting for the machine, and secondly, that it would be ineffective or harmful oftener than either manual or inhalation treatment. In its counterargument the council's[15] main contentions were as follows: that Coryllos's[16] work convinced the council that this apparatus was of life-saving value—the council quotes from a reference that is the same as one from which Henderson quotes as showing the device to be harmful; that artificial respiration plus an inhalator takes two trained men to operate, whereas the resuscitator can be managed by one; that the resuscitator is more practical to use on a pregnant woman or on a person with fractured ribs; that, "they [trained men] demonstrated completely their ability to use this apparatus to the complete satisfaction of the committee." However, devices such as the Pulmotor or "resuscitators" are not recommended by large public-utility companies, any government bureau, or the American Red Cross. Mr. James L. Fieser,[17] vice-chairman of the American Red Cross, has made the following statement:

> We believe the prone-pressure method to be the best system of producing artificial respiration for our use, particularly because of its adaptability to the character of the people to whom our life-saving and first-aid instruction is given and because it is always ready for use by anyone instructed in its performance. For these reasons the purchase of mechanical resuscitation devices is not considered a proper expenditure of chapter funds.

Mechanical External-Pressure Respirators

Respirators, such as the Drinker, Emerson and others, or tilting tables may be used for continuous applications of artificial respiration for long periods of time. These are not first-aid appliances, but hospital equipment. In some cases of carbon monoxide poisoning, especially those complicated by drugs or alcohol, a very long period of artificial respiration and inhalation may be necessary; such patients should be transported to the nearest hospital that has a machine of this type.

Artificial Respiration during Transportation

It is not generally realized that manual artificial respiration, with or without inhalation treatment, can be carried on in an ambulance.[18] In the past, just criticism has occasionally arisen because of the fact that patients undergoing artificial respiration lost their chances of recovery when ambulance crews took them to a hospital before artificial respiration had been given sufficient time to prove or disprove its utility. In cases that have to be moved, the treatment should be kept going in the ambulance, and the victim should be placed in a respirator or manual artificial respiration should be continued as soon as the hospital is reached. In such cases the necessary lapses in treatment must be as short as possible. For example, after stopping treatment to put the victim on a stretcher, treatment should be given for two or three minutes before picking up the stretcher. Again, treatment should be resumed after coming down one flight of stairs and before starting another. Each interval of cessation of treatment should not be longer than thirty seconds.

319 Longwood Avenue

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 26501

PRESENTATION OF CASE

A seventy-year-old housewife entered the hospital complaining of substernal pain of five days' duration.

Three years before admission the patient came under observation in the Out Patient Department for diabetes mellitus. This was controlled satisfactorily with daily injections of 12 to 16 units of protamine insulin and an average caloric intake of 1367, made up of 104 gm. of carbohydrate, 69 gm. of protein and 75 gm. of fat. She carried on without incident until two years before admission, when she caught a cold and came to the Out Patient Department two weeks later complaining of asthma and evening dyspnea. It was found also that she had had a nonradiating, substernal oppression on exertion and swelling of her feet for a year or more. On examination the patient was able to lie flat without difficulty. The left border of the heart was 10.5 cm. from the midline, and the rhythm was regular. The sounds were rather distant; the aortic second sound was greater than the pulmonary second, and there was a systolic murmur at the base. The blood pressure was 200 systolic, 110 diastolic. Rales were heard at the lung bases posteriorly, and there was moderate pitting edema of the shins. With rest, and decreased fluid and salt intake, her condition improved, though the blood pressure always remained in the neighborhood of 205 systolic, 115 diastolic, and her ankles became slightly swollen at night.

Five days before admission marked the onset of a severe, nonradiating substernal pain that required medication by her physician. This was accompanied by numbness in both arms, anorexia and occasional vomiting. At the time of admission the patient stated that the pain was still present, though she seemed in no acute distress.

The past illnesses and family history were irrelevant.

On physical examination the patient was a pale, obese (174 pounds) woman lying flat in bed in no discomfort. There were bilateral cataracts, which obscured the fundi. The cardiac apex was palpated 13 cm. from the midline. The sounds were regular, but of poor quality, and a loud, grating, systolic murmur, heard best in the fourth interspace 6 cm. from the midline, was transmitted in all directions. The pulmonary second sound was louder than the aortic. The blood pressure was 120 systolic, 86 diastolic; only two weeks previously it had been 180 systolic, 110 diastolic. The peripheral arteries were palpable and tortuous; no pulsation could be felt in the dorsalis pedis arteries, but the feet were warm. The pulse was regular but thready. Bubbling rales were heard at the lung bases and as high up as the scapulas. There was right-flank tenderness. Heberden's nodes were present. There was no peripheral edema.

The temperature was 100.2°F., the pulse 102, and the respirations 25.

Examination of the urine showed a ++ test for albumin, the sugar reaction was yellow, and the sediment was loaded with white blood cells. Examination of the blood showed a red-cell count of 3,740,000 with a hemoglobin of 75 per cent, and a white-cell count of 22,300 with 79 per cent polymorphonuclears. The hematocrit reading was 39 per cent, and the corrected sedimentation rate 0.9 mm. per minute. The blood sugar was 600 mg. per 100 cc. The nonprotein nitrogen of the blood serum was 85 mg. per 100 cc., and the chlorides 92.6 milliequiv. per liter.

X-ray examination of the chest showed the position of the diaphragm to be high, and there was transverse enlargement of the heart, particularly in the region of the left ventricle. The aorta was markedly tortuous, and the pulmonary vessels slightly wider than usual.

Electrocardiographic recordings showed a rate of 100 with a regular rhythm. There was moderate left-axis deviation. T_1 was upright, T_2 biphasic and T_3 inverted. There was no change in ST_1, ST_2 or ST_3. R_4 was absent, Q_4 deep and ST_4 had a high take-off. T_4 was upright.

The patient was given 15 units of protamine insulin and 20 units of regular insulin daily, but her condition was precarious from the start and grew steadily worse. For the first four days the blood sugar remained around 500 mg. per 100 cc., but the sugar reaction in the urine varied from green to orange with 0 to + test for acetone. The nonprotein nitrogen of the blood serum rose steadily. For the next two days the blood sugar fell to 236 mg. per 100 cc., but the patient continued to vomit a brown, guaiac-positive fluid. Consequently she was given dextrose and saline by clysis, and dextrose and water by duodenal tube. The patient died on the eighth hospital day, at which time the blood sugar was 752 mg. per 100 cc. with a green sugar reaction in the urine. The

nonprotein nitrogen of the blood serum had risen to 145 mg. per 100 cc.

Differential Diagnosis

Dr. Paul D. White: One of the important points of interest in this case is the common relation between diabetes mellitus and cardiovascular disease. Just this morning some of us have had the opportunity of listening to Dr. Paul Harrison, of Arabia. This sort of patient would not be met with in Arabia. Diabetes practically does not exist there, nor hypertension, nor some of the other conditions found in this case. There are thus certain advantages as well as disadvantages in living in Arabia.

This woman's substernal pain lasted five days. That is a long time. One would like to know, and there is a little more information later, whether the pain was continuous or came in waves, and whether it was paroxysmal. I might add that at the age of seventy, as Dr. Mallory has often pointed out, we should expect to make multiple diagnoses. Is it over fifty that you think one should make more than one diagnosis, Dr. Mallory?

Dr. Tracy B. Mallory: I think sixty is perhaps a safer dividing line.

Dr. White: We do not know how long she had had diabetes, nor can we dismiss it as mild, since she required insulin at this age.

One wonders whether the asthma was related to the cold, or whether some other factor such as cardiac weakness was behind it. We cannot tell with certainty from the available information. There is a fair story of angina pectoris.

Edema of the feet in a person as heavy as this patient may be due simply to a local circulatory fault with varicosities. Of course one has to think of weakness of the heart muscle, but the great majority of patients in the Out Patient Department here who come in with bilateral edema of the feet have no heart disease. Evidently this patient had no serious left or right ventricular failure.

One would like more description of the murmur. Was it louder in the pulmonic area? It might have been, as recorded here, either an unimportant physiologic pulmonary systolic murmur or it might have been the important murmur of aortic stenosis. However, the aortic second sound was apparently quite loud, a strong point against a marked degree of aortic stenosis.

With this blood-pressure reading, hypertension has to be added to the diagnoses of diabetes and cardiac enlargement. An astonishing number of persons with left ventricular weakness fail to show rales in the lung bases; they are much more often found in infection. Of course the patient had had a cold. Rales are also often heard in cases of pulmonary embolism. There can be multiple pulmonary emboli with rales at the lung bases simulating congestive failure. Or they may mean atelectasis. However, here they should be heeded in view of the story of dyspnea and swelling of the feet and moderate pitting edema of the shins.

Up to this point I think we are justified in considering that the patient had diabetes, hypertensive heart disease with effort angina pectoris, probably on the basis of coronary disease, and possibly also some weakness of the heart muscle.

Then comes the story of the acute onset of the severe present illness. I judge that she must have been given morphine. Pain is usually severe if it spreads to both arms. There is no statement of one arm's being affected more than the other. This pain was more likely due to coronary involvement than to other trouble in the chest, especially since both arms were involved. The vomiting could have been produced by the medication. It is commonly so in cases that I have seen. Patients usually vomit because of the morphine rather than from the coronary thrombosis, although some persons will vomit when they have a cardiovascular attack of any sort. This pain was of unusually long duration. The story to date sounds like that of an acute coronary thrombosis, despite the unusually long-continued pain. We must think of other conditions, but none of them seem likely.

The cardiac apex was palpated 13 cm. from the midline. That is increased 3 cm. However, one may question this measurement. The systolic murmur described is an unusually loud one. The quality is striking.

Dr. Sedgwick Mead: It was first described in the Out Patient Department, and at that time it was noted that there was a systolic murmur at the base, which was not striking. When the patient was admitted to the ward we assumed there had been an increase in intensity. It was widely transmitted and so loud as to give rise to the question of aortic stenosis.

Dr. White: Was there a thrill with it?

Dr. Mead: No.

Dr. White: It was in the fourth space, out toward the apex. That is an unusual site of maximum intensity for the murmur of aortic stenosis, but it may be widely heard and sometimes is better heard at the apex than at the base, although that is not the rule. If there had been a change and this murmur became so striking, one must think of the development of something else like a valve lesion, a rupture or injury, or a septal de-

fect resulting from myocardial infarction. These are quite rare but are on record. I have seen one or two that I think might have been such, but without autopsy. In these cases we may not be able to decide, following myocardial infarction, whether there is simply a dilated heart with mitral regurgitation or rupture of the septum, which would give a murmur something like a Roger murmur to the left of the sternum in the fourth interspace. The latter is a distinct possibility here, but it is very rare.

With the difficulty in feeling the foot arteries, one must think of intrinsic aortic abnormalities. Coarctation of the aorta would be unusual in an old person, although it has been reported at ninety. Dissecting aneurysm is a little more likely and might also explain the pain. Dissection of the aortic wall may block the pulse to the feet. However this patient's feet were warm, the pulse was regular but thready, and she was very ill at this time. There was no extreme tachypnea, perhaps helping to rule out intrinsic pulmonary disease or pulmonary embolism, although one may have a relatively slow respiratory rate with pulmonary embolism.

There was a higher leukocytosis than is ordinary for coronary thrombosis, although we see it infrequently as high as 20,000.

"The aorta was markedly tortuous." That is what we should expect. It was apparently not wide, and the diagnosis of dissecting aortic aneurysm is not supported. This week Dr. Schatzki pointed out to us very interesting comparative x-ray films of patients before and after the development of dissecting aortic aneurysms; usually there is a clear indication of such a lesion by x-ray.

We might have suspected with such a large heart and hypertension of long standing that the T waves in Lead 1 would be inverted rather than upright, and that T_3 would be upright rather than inverted. As a matter of fact, this record does not show left-axis deviation.

Dr. Mead: This description is from an electrocardioscopic examination that I made in the Emergency Ward and was not apparent in the next few tracings taken, but this is substantially what was observed at that time, and I was especially struck by the high ST segment in Lead 4.

Dr. White: There are two records here, and they are rather different. What is the time relation?

Dr. Mead: Two or three days apart.

Dr. White: These are very puzzling records but support the probability of coronary involvement, especially because of the absent R waves and high ST segments in Lead 4. The tracing looks like one of a mixed type, perhaps due to an infarction in more than one spot or else very extensive.

The course here illustrates the difficulty of treating an old patient who has both diabetes mellitus and a severe cardiovascular lesion. One condition reacts unfavorably on the other and tends to retard or to prevent the recovery. We have fairly clear evidence here of cardiac enlargement due mostly to hypertension with coronary disease and diabetes. The difficult questions concern chiefly the cause of the pain of five days' duration, the unusual murmur that was heard on the second occasion, and the electrocardiographic abnormalities. I think we should expect to find coronary thrombosis, probably an old lesion, in addition to a new one with myocardial infarction. I should hesitate to place the infarct exactly, but it may have involved both the anterior apical portion of the left ventricle and the septum, and I shall take a chance on the possibility of there having been a perforation of the septum secondary to such a lesion but shall not rule out entirely the possibility of aortic stenosis that had not been evident previously, or at least had not been well enough described for diagnosis. Once in a while myocardial infarction involves the papillary muscle, which allows the rapid development of mitral regurgitation of high degree with a sudden appearance of a loud systolic murmur that one would expect to hear maximally at the apex. We have to consider that as a possibility. Finally, simply acute left ventricular dilatation secondary to coronary thrombosis can produce a fresh mitral systolic murmur. I should put as least likely a dissecting aneurysm of the aorta.

Clinical Diagnoses

Uremia.
Chronic vascular nephritis.
Diabetes mellitus.
Arteriosclerosis.
Myocardial infarction?

Dr. White's Diagnoses

Hypertensive, coronary heart disease, with acute coronary thrombosis and large or multiple myocardial infarction involving the anterior apical portion of the left ventricle and probably the septum.
Acute perforation of the interventricular septum secondary to infarction, or acute relative mitral insufficiency secondary to involvement of the papillary muscles or simply to left ventricular dilatation.
Aortic stenosis?
Diabetes mellitus.

Anatomical Diagnoses

Coronary thrombosis, left descending.
Myocardial infarction.
Cardiac dilatation, left ventricle.
Pulmonary congestion, slight.
Arteriosclerosis, marked: aortic, coronary and cerebral.
Obesity.
Hyalinization of islets of Langerhans (diabetes mellitus).
Cerebral atrophy, slight.
Gastritis.
Leiomyoma uteri.
Melanosis coli.
Endometrial polyp.

Pathological Discussion

Dr. Mallory: The autopsy showed an enlarged heart, weighing just over 400 gm. The coronary arteries showed extensive atheroma, and there was a point of complete occlusion due to a fairly recent thrombus in the descending branch of the left coronary artery. This had resulted in a large area of infarction at the apex of the left ventricle. The ventricle appeared diffusely dilated and particularly so at its apex, a condition that, if more marked, might have led us to talk about cardiac aneurysm. The myocardial wall at the apex was soft, discolored and thinned to 5 mm., whereas at the base of the heart it measured 18 mm. and was clearly hypertrophied. Microscopic sections through the area of infarction showed complete necrosis of the muscle cells, and the end of a polymorphonuclear reaction with leukocytes that were almost all necrotic, but as yet little in-wandering of mononuclear cells. The findings all seem consistent with a history pointing to infarction of a little less than two weeks' duration. The kidneys were of the ordinary hypertensive type. The pancreas on microscopic examination showed hyalinized islets of Langerhans, which we always hope to find in diabetes but frequently do not.

I neglected to speak of the aortic valve. Evidently that was examined with considerable care, I imagine at the urging of the clinician. We finally found very slight interadherence of two of the cusps, but the diagnosis of aortic stenosis was not made.

Dr. White: Was the papillary muscle involved?

Dr. Mallory: No, and the interventricular septum was only slightly so.

Dr. White: Probably the murmur was the result of dilatation of the heart, resulting from the infarct, which thus secondarily caused mitral regurgitation, even though the reported location of the maximal murmur was unusual.

Dr. Mallory: It hardly seems as if the anatomical findings in the aortic valve explained the murmur, although one cannot say it was absolutely normal.

CASE 26502

Presentation of Case

A sixty-three-year-old blacksmith entered the hospital complaining of pain in the left chest.

Five months before admission the patient began to suffer from sharply localized pain and tenderness in the region of the third left rib close to the sternum, which radiated to the left shoulder blade. The pain was aggravated by deep breathing and coughing and was accompanied by a generalized weakness. It was constantly present as a dull ache and sometimes became severe. In addition he noticed "muscle pains" in both legs, which varied in location and intensity. For some years he had been examined every spring by his physician, and four months prior to entry albumin was found in his urine. Thereupon he consulted two other physicians, and all three made a diagnosis of Bright's disease. Three months before admission for a period of several weeks he had felt nauseated and frequently vomited after meals. Six weeks before admission a constant severe pain developed in the right subcostal region. It was aggravated by deep respiration, coughing, bending over and damp weather, compelled him to sleep on his right side or back, and often awakened him at night. A nocturia of three times a night developed. He had lost 50 pounds since the onset of his symptoms and for the past two months had had constipation, which required saline laxatives for relief. For the past month he had often felt "shivery" and needed more clothing for warmth. Three days before admission he vomited without nausea.

The patient had had arthritis at thirty-five. The family history was irrelevant.

On physical examination the patient was pale, appeared tired and showed evidence of weight loss. The breath had a uriniferous odor. The mucous membranes were pale, and the scleras slightly icteric. Numerous soft, painless, freely movable, discrete tumors measuring up to 3 cm. in diameter were present over the entire body and especially over the chest and abdomen. These were consistent with multiple subcutaneous lipomas. Over the third left rib 4 cm. from the midline there was a sharply defined, depressed, 3-cm. area of tenderness. Palpation of this area revealed mobility and crepitation of the underlying rib, and, on auscultation, crepitus could be heard on inspira-

tion. There was pain on pressure over the lower fourth and fifth ribs anteriorly. The heart was slightly enlarged to percussion, and a systolic murmur was heard over the entire precordium and transmitted into the axilla; the blood pressure was 140 systolic, 70 diastolic. The abdomen was negative except for slight tenderness over the left side. There was a left hydrocele. Rectal examination was negative. The fundi were negative, except for slight tortuosity of the vessels. Examination of the nervous system was negative.

The temperature was 100°F., the pulse 90 and respirations 20.

Examination of the urine showed a ++++ reaction for albumin, with an Esbach quantitative albumin of 8.0 gm. per liter. There were numerous granular and a few cellular casts and 10 to 15 white blood cells per high-power field. Bence-Jones protein was never demonstrated, and cultures were negative. Examination of the blood showed a red-cell count of 2,000,000 with a hemoglobin of 50 per cent, and white-cell count of 7800 with 73 per cent polymorphonuclears, 15 per cent lymphocytes, 1 per cent eosinophils and no basophils. The red cells showed a marked variation in size and shape. An occasional plasma cell was reported in the blood smear. The nonprotein nitrogen of the blood serum was 115 mg. per 100 cc., the proteins 6.7 gm., the calcium 10.9 mg., the phosphorus 10.5 mg. and the phosphatase 3.3 units. A blood Hinton test was negative. Examination of the stools was negative.

X-ray examination of the skull showed three or four small areas of decreased density. There was marked destruction, with pathologic fracture, of the seventh dorsal vertebra. An area of destruction involved the ninth rib on the right, with increase in the size of the rib in the area of destruction. An area of destruction also involved the vertebral end of the ninth rib on the left side, with increase in the size of the rib in the area of destruction. There was localized new-bone formation about the articulations of the right fourth and fifth lumbar vertebrae. The femurs showed a number of minute areas of rarefaction just above the condyles, and the arteries of the leg showed advanced calcification. X-ray examination of the chest showed a soft-tissue thickening of the anterior extremity of the third left rib, but the underlying bone appeared normal. There was a sharply defined area of rarefaction in the lateral extremity of the left clavicle, and also an indefinite area of rarefaction in the mid-shaft of the right clavicle. The aorta showed a marked degree of tortuosity, and there was a suggestion of a mass at the left hilum. The peripheral portions of the lung fields were clear.

An intravenous pyelogram showed the kidneys to be normal in size, shape and position. Films taken up to forty minutes after injection of the dye showed no excretion on either side.

A gastrointestinal series at another hospital showed a normal esophagus, stomach and small intestine.

Eight days after admission the blood chlorides were 117 milliequiv. per liter, and the carbon dioxide combining power 11.1 milliequiv., and the nonprotein nitrogen had risen to 170 mg. per 100 cc. The patient failed rapidly and died on the eleventh hospital day.

Differential Diagnosis

Dr. James R. Lingley: These shadows in the skull are rather indefinite, but I think that there are a few small areas of rarefaction, two in the frontal region and one in the temporal. The most obvious lesion demonstrated on the films is the destroyed vertebra. The width of the body is markedly reduced. There is a definite pathologic fracture without any new-bone formation, and the intervertebral spaces above and below are preserved. The ninth rib shows some expansion near its articulation to the spine, as described, and there is also destruction of the transverse process of the ninth vertebra. Both femurs show very minute areas of rarefaction just above the condyles. These may be pathologic but could be due to atrophy. It would be unusual for atrophy, however, since the rest of the bones appear normal.

Dr. Alfred Kranes: Does the rest of the skeleton appear normal?

Dr. Lingley: Yes. The chest shows a mass superimposed on the left hilum and arch of the aorta. In the lateral view it is not well visualized, but it probably lies posterior to the root of the lung and therefore represents a paravertebral mass rather than one due to lymph nodes at the hilum.

Dr. Kranes: Then you do not believe it is in the lung?

Dr. Lingley: I doubt it because the lungs are clear in the lateral view. I believe they are normal.

Dr. Kranes: After reading this record we can be reasonably sure that this patient suffered from two conditions: a fairly advanced degree of renal insufficiency, and a malignant neoplasm of some type. Our problem seems equally clear cut, namely, to determine whether these two processes were independent of each other or related, and in addition to discuss the nature of the renal and skeletal lesions. And because Dr. Mallory has asked us to be brief, I shall confine my discussion only to a consideration of the more relevant possibilities and omit those that seem more remote.

We first have to consider whether the kidney

disease was independent of the skeletal disease, and if we assume that it is, we have to make a diagnosis of some sort of primary nephritis. It seems to me that the evidence in favor of such a diagnosis is very meager. We are fortunate in being told that this patient had been repeatedly examined by his physician, and at no time before his present illness were abnormalities of the urine demonstrated. I assume that the urine was examined, and it was not until four months before admission that albumin was found. It therefore seems unlikely that the patient had any preexisting renal disease. Furthermore, the renal process did not behave like any of the chronic renal diseases, such as chronic glomerulonephritis, vascular nephritis and pyelonephritis. There is no hypertension, no evidence of cardiac enlargement by x-ray, although the physical examination showed the heart to be a little large, and no arterial changes except in the large vessels of the leg. Consequently I think any primary renal disease is improbable. Furthermore, one would like to cover the whole picture with one diagnosis if one could. So I shall go on and assume that both the renal and skeletal lesions were part and parcel of the same disease.

We then have to consider what types of malignant neoplasm will cause renal insufficiency. There are two ways in which cancer can cause renal insufficiency. One is by destruction of the renal parenchyma, and the other by obstruction of the urinary tract, either the urethra or both ureters. So far as the destruction of the renal parenchyma goes, I think it is highly improbable that any cancer would do that. A hypernephroma for example is almost always unilateral, and it would be unique for a hypernephroma or primary renal-cell carcinoma to destroy enough renal tissue to produce uremia. The same would be true of metastatic lesions to the kidney.

We come then to the possibility of obstruction to the urinary tract by cancer. In the male the two most frequent lesions producing urinary obstruction are carcinoma of the prostate and carcinoma of the lower gastrointestinal tract invading the pelvis and obstructing both ureters. So far as the prostate goes, one must admit the possibility of a small lesion in the prostate, not clinically obvious, which could produce this clinical picture. I think, however, that if it were extensive enough to produce urinary obstruction one would be able to feel something more than was felt by rectum in this patient. The same I think holds true for cancer of the gastrointestinal tract with pelvic metastases: one should be able to find some evidence of pelvic metastases by rectal examination. Furthermore, I think the urinary picture is not that of urinary obstruction. If that were the case one would expect a decrease in urinary output, whereas this patient developed a polyuria. Nor is the urinalysis what one would expect with an obstructive lesion somewhere in the genitourinary tract. Eight grams per liter is a lot of albumin, and one ordinarily does not expect that amount of albuminuria with any obstructive lesion.

There is one disease that does explain this picture, and that is multiple myeloma. Whenever one is confronted with a disease with widespread involvement of the skeleton and also renal insufficiency of an unusual type, as I think we have here, one should always first consider multiple myeloma, the renal lesion, as you know, being due to deposits of Bence–Jones protein in the tubules. On the whole I think that is the best diagnosis I can make. In this particular case it may seem unwise to make that diagnosis in the absence of any confirmatory laboratory evidence. One would expect in repeated search that Bence–Jones protein might be found, but there are a considerable number of cases in which no Bence–Jones protein can be demonstrated. Nor does the normal serum protein exclude it. It is elevated in only half the cases. The fact that an occasional plasma cell was found in the blood does not mean much because that might be found in any blood.

There is one other disease that must be considered. Whenever we are confronted with the combination of skeletal and renal lesions, the question of hyperparathyroidism must be raised. But I think the evidence against it is too great in this case. The x-ray pictures show localized areas of destruction with intervening normal skeleton. One would not expect such localized lesions in hyperparathyroidism. Furthermore, the type of renal insufficiency here is not what one would expect with hyperparathyroidism in which the renal failure is due to one of two causes, either bilateral stones, of which there is no evidence, or calcification of the renal tubules, which, if it were extensive enough to cause such marked renal failure, might be expected to show by x-ray. So far as the chemical constituents of the blood are concerned, the pattern may have been masked a great deal by the renal insufficiency. A patient with hyperparathyroidism may have a low serum phosphorus, but when renal failure develops it rises. Similarly one may ask if a calcium of 10.9 mg. in a patient with marked renal failure does not actually represent an elevation of serum calcium, because ordinarily the calcium goes down in uremia. Considering all these possibilities I shall

make a diagnosis of multiple myeloma, with renal insufficiency due to myeloma kidneys.

Dr. Bernard Jacobson: How does Dr. Kranes conceive of Bence-Jones kidneys without Bence-Jones protein in the urine?

Dr. Kranes: I think that in some of the cases we have seen here Bence-Jones protein was not demonstrated in the urine, but the kidneys did show deposits in the tubules at autopsy.

Dr. Jacobson: Of the cases of myeloma about half died finally in uremia, and of some 8 or 9 cases that have died of uremia under our own eyes, all have had Bence-Jones protein in the urine during life. I agree with Dr. Kranes that the occasional plasma cell in the blood is normal.

Dr. John W. Zeller: Is not amyloid disease of the kidney present in myeloma?

Dr. Tracy B. Mallory: Certainly not usually. It may be.

Dr. Lingley: The minute areas of rarefaction in the lower femoral shafts interest me very much. Dr. Jacobson and I have been reviewing the cases of myeloma observed here during the last few years, and we think that, in some cases, these minute areas of destruction are one of the earliest roentgenological signs. They are extremely small and punctate, and unfortunately they usually cannot be differentiated from atrophy. In this case there is one small, oval area of rarefaction in the left clavicle that is more characteristic.

Clinical Diagnoses

Multiple myeloma.
Chronic nephritis.

Dr. Kranes's Diagnoses

Multiple myeloma.
Myeloma kidneys.

Anatomical Diagnoses

Multiple myeloma.
Pathologic fractures of the third left rib and seventh dorsal vertebra.
Myeloma kidney.
Acute pyelonephritis.
Hypertrophy of the heart.

Pathological Discussion

Dr. Mallory: At post-mortem examination the most obvious lesions were in the skeletal system. The sixth, seventh and ninth ribs on the right and the third and fourth ribs on the left showed localized tumors. These for the most part lay within the marrow cavity and had expanded and thinned the cortex. In one place the tumor had produced a pathologic fracture, and in another it had broken through to form a mass 2.5 by 3 cm., which entirely surrounded the rib. The bodies of two vertebrae were entirely filled with tumor, one of them, the seventh dorsal, showing a compression fracture. From the margins of this vertebra two large paravertebral masses of tumor projected to either side of the spine. As is usual with myeloma no visceral metastases were found.

The other point of interest was, of course, the status of the kidneys. They were of normal size, weighing 350 gm., but the cortices were narrowed to 3 or 4 mm. The capsules stripped readily, revealing smooth surfaces mottled with irregular pinkish-gray patches. The cut surfaces showed similar mottling, and the gross appearances were thought to be suggestive of pyelonephritis, though there was no dilatation of the pelves or injection of their mucosa. The microscopic sections are not easy to interpret. There is evidence of considerable arteriolar sclerosis and of patchy atrophy of the cortex. There are a few small acute abscesses. The unusual feature is the abundance of dense hyaline casts in all parts of the tubule system. These might be interpreted either as the "colloid casts" of chronic pyelonephritis or as the coagula of Bence-Jones protein that plug the renal tubules in so many cases of myeloma. There is unfortunately no specific method of differentiation. Two points incline me to the second hypothesis; first, the casts are diffusely scattered throughout the tubule system rather than being concentrated in focal areas and, secondly, some of the casts are surrounded by foreign-body giant cells. This giant-cell reaction is very frequent in the myeloma kidney, whereas I cannot remember to have observed it in pyelonephritis. I am therefore going to side with Dr. Kranes against Dr. Jacobson. I should not be surprised, however, to find that other pathologists might disagree with my interpretation. Certainly in view of the scattered small acute abscesses we must admit some degree of terminal pyelonephritis as well.

The New England
Journal of Medicine

Formerly the
Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
The New Hampshire Medical Society
The Vermont State Medical Society

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Subscription Terms: $6.00 per year in advance, postage paid, for the United States; Canada, $7.04 per year; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Saturday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

TRUETA'S TREATMENT OF COMPOUND FRACTURES

Now that our country is mobilizing in preparation for all eventualities, including war, it behooves the medical profession to be prepared technically as well as spiritually for any contingency. A great contribution to military surgery has come out of the recent Spanish War, the major lessons of which have been covered in a small book by Trueta,[1] of Barcelona.

During World War I, surgeons became antiseptic nihilists, and long before the war was over the principle of thorough débridement for traumatic injury to the body was well established. When the Spanish War broke out, the surgeons began at the point where they had left off. In the previous war the most unsatisfactory surgical procedure was the treatment of compound fractures. As a rule, the extremities were kept in some form of traction apparatus, and the wounds were left open after being thoroughly débrided and were then dressed frequently, with or without irrigations consisting of a neutral sodium hypochlorite (Carrel–Dakin) solution.

A few exceptions to this care of compound fractures occurred, principally one adopted by Rutherford Morrison, of Newcastle, England. After débridement, Morrison introduced "BIP" (bismuth-iodoform paste) into the wound, closed the wound loosely, and then put the extremity in some form of immobilization apparatus, — often plaster, — changing the dressings infrequently. Unfortunately this method did not receive universal application, although in Morrison's hands the results were satisfactory. A few surgeons, however, — notably Orr and Baer in this country, — continued the procedure of immobilization as a primary requisite for the proper treatment of fractures of the extremities.

Gamgee as early as 1853 advocated the fixation and infrequent dressing of wounds complicated by fractures. Curiously, when Lister introduced antisepsis, a good deal of this idea was lost and, indeed, did not reappear in force and well supported by data until the Spanish surgeons proved the greater efficacy of the immobilization method. Perhaps our Spanish colleagues found themselves without fixation apparatus other than plaster of Paris, or perhaps immediate débridement and complete immobilization of all compound fractures seemed to be the wisest method of procedure in bombed cities, where, incidentally, the wounds were probably less seriously contaminated than those seen by most military surgeons in World War I. Whatever the impetus to this method of therapy, it must now be accepted as vastly superior to any as yet practiced by the military surgeon.

Trueta's monograph reports 1073 cases of compound fracture of the limbs, most of them war wounds. The 976 good or satisfactory results, with 6 fatalities, are better by far than anything previously accomplished. He gives a complete re-

view of the method used by the Spanish surgeons. In brief, the technic recommended for the immediate treatment of war fractures is as follows: immediate careful débridement of the wound, which must consist in excision of the skin edges and in the removal of all contused and damaged tissue, displaced or completely denuded bony fragments, and foreign bodies; complete immobilization of the limb in plaster of Paris, without the use of windows or bridges over the wounded area; injection of tetanus antitoxin; drainage, depending on the seriousness of the damage and the time since the injury; the skin should be left open, or if closed, the sutures must be few and allowance must be made for the discharge of material under the cast.

Of course the success of this therapy lies in early application. Obviously under the conditions of an air-raid where the patient is seen within an hour, the wound does very well; but the longer the interval between the injury and surgical attention, the less frequently this treatment can be followed. Trueta makes the statement that when the infection is gross and the cellulitis widespread, immediate surgery and immobilization in a closed cast cannot be resorted to. His usual technic, however, may somewhat alter the plans of the medical department of an army; for if such fractures are best treated by immediate immobilization, surgical teams should be far nearer the scene of bombing than ever before. Once a patient is in a plaster cast he is easily and simply transported.

In speaking of the value of immobilization of such compound fractures, Trueta emphasizes that rest allows the formation of local venous and capillary thrombi, thus preventing the spread of infection, and the formation of new capillaries, thus hastening healing. In fact this method is a criticism of the conscientious surgeon who, meaning well, dresses wounds so frequently that they cannot heal.

In speaking of the discharge from the wound that necessarily occurs beneath the plaster, Trueta lists the bad odor as the chief deterrent. This indeed was so great in the hot weather that casts had to be changed earlier than the surgeons desired. As a rule the first cast is changed in ten or fifteen days, the second is left on for twenty or thirty days and the third is left on until healing is complete — in many cases for more than two months.

American observers[2] have confirmed the results of the Spanish surgeons, and there can be little doubt that the method henceforth should have the widest application. All surgeons contemplating military service should be familiar with this advance in the treatment of compound fractures.

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MEDICAL EPONYM

FLAJANI'S DISEASE

The classic Italian description of toxic goiter is that of Giuseppi Flajani (1741–1808). The following translated extract is taken from an observation entitled *"Sopra un tumor freddo nell' anterior parte del collo detto broncocele* [Regarding a cold tumor in the anterior part of the neck, called a bronchocele]" in his book, *Collezione d'osservazioni e riflessioni di chirurgia (Collected Surgical Observations and Reflections)* (Rome, 1798–1803: Vol. III, p. 271).

> There suddenly appeared in the anterior part of the neck of one Giovanni Spagnolo a tumor that in the course of four months grew to a considerable size so that it occupied the anterior and lateral aspects of the neck. He was under the care of his physician during a period of seven months, not so much because of the swelling as on account of the difficulty in breathing, continuous dyspnea and marked palpitation in the region of his heart. In the attempt to lessen these symptoms, the man had been obliged to abandon his occupation as a painter and to lead a life of idleness, thinking to avert an incurable organic condition.
>
> Giovanni being then twenty-two years of age and being persuaded of the seriousness of his malady, requested some remedy by which the tumor might be lessened in size or by which its growth might at least be impeded, since it seemed that its pressure on the subjacent parts was gradually causing more difficulty in breathing and speaking. This was the story that the physician-in-charge gave me when I was called to see the patient. On inspection, the tumor seemed to be of considerable size and was apparently divided into two parts by a sort of central cleft. Externally the color was normal except for the veins, which were swollen as if varicose. There was no tenderness to touch, although pressure with the fingers caused difficulty in breathing. He was exhausted and emaciated, possibly because of frequent bleedings, to which he had been obliged to resort at least once a month.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
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DIABETES DEVELOPING DURING PREGNANCY, COMPLICATED BY HYDRAMNIOS

Mrs. C., a thirty-two-year-old primipara, was first seen on July 3, 1939, when approximately thirty-six weeks pregnant. She was referred by her family physician after a borderline diabetes had been discovered in the thirtieth week of pregnancy. This condition was being followed by a specialist in diabetes and was controlled by small doses of insulin.

The family history was noncontributory. The patient had an appendectomy at the age of nine, and a tonsillectomy at twenty. She also had had measles and chicken pox. Catamenia began at fourteen, were regular with a twenty-eight-day cycle and lasted five days without discomfort. The last period began at the end of October, 1938, making the expected date of confinement early in August.

Physical examination revealed a well-developed and well-nourished woman. The weight was 133 pounds, a gain of 23 pounds over her normal weight. The heart was not enlarged; there were no murmurs. The lungs were clear and resonant; there were no rales. The blood pressure was 112 systolic, 70 diastolic. Abdominal examination revealed a fundus which was 29 cm. above the symphysis; the vertex was at the pelvic brim. The fetal heart was heard. Vaginal examination revealed an almost flat cervix, which was dilated to admit one finger. It was believed that labor would occur in about two weeks.

The patient was seen again by the obstetrician on July 6 and July 11. At neither of these visits was there any evidence of edema or elevation of the blood pressure. Blood-prolan tests were normal.

On July 16 a vaginal examination revealed that the cervix was favorable for induction; the membranes were ruptured artificially, with the escape of a large amount of fluid. Labor started immediately, and in eight hours the patient was delivered by a simple forceps operation of a male child weighing 9 pounds, 3 ounces. The baby was in good condition.

The mother made an uneventful convalescence; she did not nurse. When seen in the office on August 28, the weight was 111 pounds and she seemed very well.

Comment. This is a case of diabetes that was first recognized during pregnancy. The diabetes was very mild and was easily regulated with small doses of insulin. Labor was induced three weeks early because of definite hydramnios, which is characteristic of diabetic patients, and also to avoid intrauterine death. The size of the child, 9 pounds, 3 ounces, three weeks before full gestation is another characteristic of infants born of diabetic mothers.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following session, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, has been arranged for the week beginning December 16:

BRISTOL NORTH

Thursday, December 19, at 4 p.m., at the Morton Hospital, Taunton. Gonococcal Infections in the Armed Forces and the Civil Population. Instructor: Oscar F. Cox. Lester E. Butler, *Chairman.*

DEATHS

GAFFNEY — MARY E. GAFFNEY, M.D., of Charlestown, died December 5. She was in her sixty-seventh year.

Dr. Gaffney received her degree from Tufts College Medical School in 1907, and was a former member of the staff of the Rhode Island State Sanatorium, Wallum Lake. She was a former member of the Massachusetts Medical Society and had retired from active practice.

MELLUS — EDWARD MELLUS, M.D., of Newton, died December 7. He was in his sixty-ninth year.

Born in Zumbrota, Minnesota, he attended Worcester High School and Harvard College, and received his degree from the Harvard Medical School in 1903. He was a member of the Massachusetts Medical Society and the American Medical Association. He was also a member of the Newton Board of Health, a member of the staff of the Newton Hospital, a former member of the city planning board, and a member of the New England Society of Psychiatry. At the time of his death he was treasurer of the Middlesex South District Medical Society.

Dr. Mellus maintained a sanatorium in Newton until 1929, when he retired from active practice.

Two sons and a daughter survive him.

MISCELLANY

CHAPTER OF ALPHA OMEGA ALPHA AT TUFTS

On December 2, six members of the faculty and ten fourth-year students at Tufts College Medical School were initiated as charter members of Beta Chapter of Alpha Omega Alpha, the national honorary medical society. Dr. Walter L. Bierring, former president of the American Medical Association and national president of Alpha

Omega Alpha, conferred the charter. It was accepted on behalf of the school by Dean A. Warren Stearns. Certificates and keys were presented to the initiates by Dr. Josiah J. Moore, national society secretary.

Guests were Dr. Reginald Fitz, Dr. Walter B. Cannon, Dr. Henry A. Christian and Robert S. Grier, of Harvard Medical School, Dr. Hardy A. Kemp, dean of the University of Vermont Medical School, and President Leonard Carmichael, of Tufts College. Dr. Hyman Morrison, professor of clinical medicine, served as chairman of the faculty committee on installation.

The faculty initiates were as follows: Dr. David D. Berlin, professor of clinical surgery; Dr. Abraham Myerson, professor of neurology, emeritus; Dr. Dwight O'Hara, professor of preventive medicine; Dr. Alonzo K. Paine, professor of obstetrics; Dr. Louis E. Phaneuf, professor of gynecology; and Dr. Stearns, dean and professor of neurology.

The student initiates were as follows: Carl J. Antonellis, of Medford; Carroll J. Bryant, Jr., of Indian Orchard; George A. Dodge, 2d, of Brookline; Clement S. Dwyer, of Boston; Jesse G. Garber, of Brookline; Herbert F. Hager, of Providence, Rhode Island; Alfred Kant, of Cranston, Rhode Island; Arthur N. Kelly, of East Boston; John L. O'Hara, of Newton; and Raymond Yesner, of Boston.

INCIDENCE OF TUBERCULOSIS AMONG UNIVERSITY STUDENTS

A study of tuberculosis among students at Lund University in Sweden by Hedvall (The incidence of tuberculosis among students at Lund University. *Am. Rev. Tuberc.* **41**:770–780, 1940) calls attention to the great risk of tuberculosis confronting young people and describes an excellent procedure for mass surveys of students. Of special interest is the discovery that the high incidence of tuberculosis among medical students was traced to the post-mortem examinations during their course in pathology. Abstracts of the study follow:

Pulmonary tuberculosis is characterized by an insidious protracted course and a prolonged absence of clinical symptoms. When such symptoms finally appear, the changes have frequently spread extensively in one or both lungs. It is essential, therefore, that pulmonary tuberculosis should, if possible, be diagnosed before the appearance of morbid symptoms.

On registration all students are required to go to the Student's Tuberculosis Bureau for an examination. On the first visit a careful history is taken, a tuberculin test by the Pirquet method and a sedimentation test are made, together with a fluoroscopic and radiographic examination. If the tuberculin test is negative, the students are retested by the Mantoux method with from 0.1 up to 1.0 mg. tuberculin. Only those who do not react to the 1.0 mg. dosage are considered negative.

A re-examination of all students is made at least once a year and follows the procedure of the original examination, with the exception of the x-ray examination, which is done every third year. However, an x-ray film is taken when the previous history, rate of sedimentation or fluoroscopic examination indicates something suspicious or when greater caution is necessary for some other reason. When the tuberculin reaction changes from negative to positive an x-ray examination is made every third month during the first year after the primary infection and every six months during the second year, even if no changes have been demonstrated. On the other hand, if any changes are observed they are followed by means of x-rays at intervals of a few weeks or months, irrespective of expense.

Altogether 3336 persons were examined; 638 were medical students, 1367 philosophy students, 409 theology students, 488 law students. To these were added 434 probationary nurses at the South Sweden School for Nurses. They were included to obtain a comparison with the medical students, since both these groups are undoubtedly exposed to a certain risk of tuberculous infection.

Among those examined, 133, or approximately 4 per cent, were found to have active tuberculosis. Of the 133 cases, 47 were tuberculin negative and had normal lung x-ray films when entering the university or school for nurses; 43 had been infected at some period of their lives, since they were tuberculin positive on first examination but were radiologically sound; and the remaining 43 were tuberculin positive and did not show a normal x-ray picture of the lungs on first examination. Some of these already had tuberculosis, but others did not develop it until later.

In general, the tuberculous changes were progressive and significant. Of the 47 patients who showed no evidence of tuberculosis on entrance, there developed 14 cases of pulmonary tuberculosis, as well as cases of erythema nodosum, exudative pleurisy, tuberculous peritonitis and miliary tuberculosis, with 2 deaths.

Of the 43 patients in the second group who were tuberculin positive but radiologically sound on first examination, 37 developed pulmonary tuberculosis, 2 tuberculosis of the hilar lymph nodes, and 4 pleurisy. One of the cases of pleurisy developed pulmonary tuberculosis as a complication, and the patient died.

Of the 133 cases of tuberculosis found in the period from 1930 to the end of the 1937 spring term, 110 were among the university students and 23 among the nurses. Ninety-five students and 15 nurses are at present fit for work. Of the other patients, 9 have died, 5 are unfit for work and 9 are still at the sanatorium.

It is of interest, however, to know not only the number of cases found and how they developed, but also the frequency of the disease in the different groups, as shown in the table:

	No. of Persons Examined	No. of Cases of Tuberculosis Found	Percentage
Medical students	638	72	11.3
Philosophy students	1367	17	1.2
Theology students	409	12	2.9
Law students	488	9	1.8
Nurses	434	23	5.3

These figures indicate that both medical students and probationary nurses are exposed to a considerable risk of tuberculous infection.

During the first year, no case of tuberculosis was found among the medical students. In the second year 4 cases were detected and during the third to the fifth year 10 cases each year. From the sixth to the ninth year only 6, 4, 2 and 1 cases respectively were diagnosed. Thus, most of the tuberculous cases were discovered during the third to the fifth year of study, a period which coincides with the last course before and the first course after the beginning of the practical training at the hospital. Since the medical students live under practically the same conditions as other students at the university, the high tuberculosis morbidity among them must be due to a risk of infection to which they alone are exposed.

Quite a number of the medical students are primarily infected before they begin their hospital training course and, therefore, some course taken before this training must be significant. The medical students themselves

have for a long time suspected that the course in general pathology taken before the hospital duty, and lasting one year, constitutes a danger of tuberculous infection. In at least 16 cases, there is a significant connection between the course of general pathology and the appearance of the primary infection. In the other cases the primary infection occurred either before or after the pathological course, during the training at the hospital.

The infection acquired during the course in pathology may have originated from fellow-students or physicians. The probability of this happening was, however, carefully excluded. For this reason, thorough and repeated examinations of the autopsy rooms were made for the presence of tubercle bacilli. Samples were taken from towels, trays, dust on the autopsy tables and in the rooms, and it was found that in spite of all precautions during the post-mortem examinations, tubercle bacilli were discovered when an examination was made twenty-four hours after a necropsy examination of a person with pulmonary tuberculosis. In addition to guinea-pig inoculations, suitable cultural experiments were made to obtain a quantitative idea of the presence of tubercle bacilli on the objects and in the rooms examined.

As a result of these examinations, more stringent precautions in disinfecting the autopsy rooms were taken and finally it was agreed, at least for the present, to limit the necropsy examinations of tuberculous patients as much as possible. The results of the latter step are as yet available only for two terms. Nevertheless, examinations showed that for the first time all tuberculin negative reactors at the beginning of the course were also negative at the conclusion of the course. The investigation is being continued and the definite result awaited, but the author believes that he is justified in expressing the view that excessive tuberculous morbidity among medical students can be reduced by taking special precautionary measures against tuberculous infection in hospitals and in rooms in which necropsy examinations of tuberculous subjects are performed.

RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1940

Diseases	October 1940	October 1939	Five-Year Average*
Anterior poliomyelitis	7	21	58
Chicken pox	491	333	339
Diphtheria	22	24	19
Dog bite	842	823	770
Dysentery, bacillary	21	165	39
German measles	27	40	30
Gonorrhea	374	474	499
Lobar pneumonia	218	157	237
Measles	619	291	210
Meningococcus meningitis	5	5	7
Mumps	199	91	206
Paratyphoid B fever	3	3	2
Scarlet fever	265	179	348
Syphilis	394	464	453
Tuberculosis, pulmonary	256	238	259
Tuberculosis, other forms	35	32	32
Typhoid fever	8	4	8
Undulant fever	3	4	6
Whooping cough	645	346	419

*Based on figures for preceding five years.

RARE DISEASES

Actinomycosis was reported from: Swampscott, 1; total, 1.

Anterior poliomyelitis was reported from: Monterey, 1; Northampton, 1; Russell, 1; Springfield, 1; Wareham, 1; Worcester, 2; total, 7.

Anthrax was reported from: Lynn, 1; total, 1.

Diphtheria was reported from: Boston, 3; Cambridge, 2; Chicopee, 2; Cohasset, 1; Fall River, 3; Lawrence, 1; Melrose, 1; New Bedford, 1; Somerville, 4; Westboro, 2; Worcester, 2; total, 22.

Dysentery, bacillary, was reported from: Boston, 6; Cambridge, 5; Danvers, 5; Lowell, 4; Taunton, 1; total, 21.

Meningococcus meningitis was reported from: Gloucester, 1; Natick, 1; Pittsfield, 1; Reading, 1; Uxbridge, 1; total, 5.

Paratyphoid B fever was reported from: Boston, 1; Danvers, 1; Worcester, 1; total, 3.

Pellagra was reported from: Boston, 2; Greenfield, 1; total, 3.

Septic sore throat was reported from: Beverly, 1; Boston, 5; Cambridge, 2; Greenfield, 1; Lynn, 1; Somerville, 1; Sturbridge, 3; Weston, 1; total, 15.

Tetanus was reported from: Framingham, 1; total, 1.

Trachoma was reported from: Plymouth, 1; total, 1.

Trichinosis was reported from: Cambridge, 1; Framingham, 1; Lynn, 1; Webster, 1; Worcester, 1; total, 5.

Typhoid fever was reported from: Athol, 1; Boston, 2; Chelsea, 1; Malden, 1; Waltham, 2; Worcester, 1; total, 8.

Undulant fever was reported from: Shrewsbury, 1; Webster, 1; Whitman, 1; total, 3.

Anterior poliomyelitis continued to show low incidence.

Diphtheria, measles, whooping cough, chicken pox and tuberculosis (other forms) were reported above the five-year averages.

The incidences of meningococcus meningitis and undulant fever were not remarkable.

Typhoid fever was reported at a figure equal to that of the five-year average.

Lobar pneumonia, pulmonary tuberculosis, mumps, scarlet fever and German measles were reported below the five-year averages.

Dog bite was reported at a record high figure for the third consecutive month. Animal rabies showed an increased incidence with active foci in Cohasset, Attleboro, Boston and Hingham.

REPORT OF MEETING

BOSTON ORTHOPEDIC CLUB

A regular meeting of the Boston Orthopedic Club was held at the Boston Medical Library on October 21, with Dr. Augustus Thorndike, Jr., presiding. The speaker of the evening, Dr. Fuller Albright, discussed the subject, "Metabolic Bone Disease." It was initially emphasized that any metabolic disease is generalized and not, like infection or tumor, merely disseminated. At times this generalized character may be masked, particularly if the disease is more marked in localized areas. It has been found that the absence of the lamina dura of the teeth is a good index of generalized bone disease.

Dr. Albright briefly discussed the normal metabolism of bone, in which both addition and subtraction are taking place at the same time. Probably only 1 per cent of all bone is being thus actively metabolized at any time, however. The loss of calcium phosphate from bone to the surrounding fluid is governed by physicochemical laws, and the simultaneous deposition of this compound is probably due to an elevation of the phosphate ion brought about by the enzyme phosphatase.

The discussion was limited to those conditions in which too little bone is found. In the first type of disease there is too little bone formation as a result of osteoblastic hypoplasia — namely osteoporosis. This condition may be found in prolonged immobilization in a cast, which

causes lack of stimulation to the osteoblasts. There is an elevated urinary calcium and a real possibility of renal calculi. Since this is not a disease of impaired calcification but of hypoplasia of osteoblasts, theoretically there should be a low phosphatase value; however, this is normally so low that subnormal levels are almost unknown. It was pointed out that osteoporosis occurs only in the immobilized parts, so that the skull of a patient bedridden with arthritis remains normally dense, in contrast to that of one with hyperparathyroidism.

This condition is common in senescence and is also found in an idiopathic form. Further study has revealed, however, that the idiopathic type invariably occurs in women after the menopause. This was correlated with investigations in fowl, in which the bones of male doves, originally much thinner than those of females, were made thicker by the administration of estrin. The application of this clue to human osteoporosis has so far been inconclusive; for although such women remain in positive calcium balance while under estrogen therapy, there has not been any demonstrable thickening of the porotic bones. The patients have done well clinically, but this is the usual course, despite their roentgenological lesions.

Dr. Albright pointed out that the salient features of Cushing's syndrome are: an insulin-resistant diabetes; muscular weakness; a thin skin, which leads to the plethoric complexion and striae; osteoporosis, with a normal phosphatase; hirsutism, without other signs of virulism; girdle obesity, which is probably due to poor bone and muscular development; hypertension; an amenorrhea and impotence. At post-mortem examination these patients may or may not show a carcinoma of the adrenal cortex, but the 17-ketosterone assay on the urine confirms the presence of a hyperfunctioning adrenal cortex even in the absence of a carcinoma. Since one of the functions of this organ is glycoketogenesis, dysfunction leads not only to an elevated blood-sugar level but to a decreased protein content. This lack of poor building material causes osteoporosis, muscular weakness and thin skin, and one aim of treatment should therefore be to maintain a positive nitrogen balance. Testosterone, the best drug for that purpose, has been employed in treating Cushing's syndrome, with encouraging clinical results in the nonmalignant cases. Under this regimen patients have regained as much as 7 per cent of their body protein per month.

Dr. Albright next considered deficient calcification in the presence of adequate osteoid matrix, a condition exemplified by osteomalacia. This disease is uncommon in the United States and is found only in cases of steatorrhea, in which the failure to absorb fat results in fat-soluble avitaminoses, the lack of vitamin D being the important factor. There is a normal or low calcium, a low phosphate and an elevated phosphatase level.

Under the second large classification of increased bone destruction as a cause of too little bone, the speaker briefly discussed hyperparathyroidism; this hormone elevates the calcium level in the blood and urine by withdrawing it from the bone, meanwhile lowering the phosphate level. It is essentially a metaplasia of bone, with great activity of osteoblasts and osteoclasts, and a high phosphatase level when the bone is diseased. Often there is no disease, for the calcium output in the urine and feces remains fundamentally unchanged despite the intake, which is usually adequate to maintain equilibrium. The clinical manifestations center around kidney stones, and the orthopedic specialist sees only the exceptions.

In conclusion, Dr. Albright discussed a new entity, which he called "osteitis fibrosa disseminata," and which is not considered truly metabolic. Characteristically, there are predominantly unilateral lesions of a productive as well as destructive character, brown spots confined to the skin, — usually on the same side, — precocious menstruation in females, early closure of the epiphyses and normal chemical constituents in the blood. There is great density of the base of the skull, and the lesions are progressive. Practically, the dermal and menstrual characteristics may be absent, and there may be bilateral lesions. Clinically it resembles Paget's disease, but examination of the bone shows no cement lines. It cannot be classed as a dyschondroplasia because of the skull involvement, and it is not hyperparathyroidism because of the normal blood constituents and the disseminate distribution. A neurological basis was suggested to account for the segmental distribution, the spots that simulate remotely those of neurofibromatosis, and the gonadal dysfunction. The latter was explained by a lesion or dysfunction of the hypothalamicohypophyseal tract.

NOTICES

ANNOUNCEMENT

AGNES A. NERSESSIAN, M.D., announces the removal of her office from 153 Nahatan Street, Norwood, to 525 Washington Street, Norwood.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse under Alexander Thiede, formerly concertmaster of the Cleveland Symphony Orchestra, every Thursday at 8:30 p.m. Those interested in becoming members should communicate with Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

There will be a meeting of the New England Society of Physical Medicine at the Hotel Kenmore, Boston, on Wednesday, December 18, at 8:00 p.m. An informal dinner will be held in the Empire Room at 6:30 p.m.

PROGRAM

The Latest Developments in Physical Medicine at the Massachusetts General Hospital (with slides). Dr. Arthur L. Watkins.

Thermal Exchange During Applied Radiation (with slides). Dr. John G. Gibson, 2d.

All members of the medical profession are cordially invited to attend.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The fall meeting and dinner of the Massachusetts Society of Examining Physicians will be held at the Copley-Plaza Hotel, Boston, on Wednesday evening, December 18. Dinner, at $2.50 per plate, will be served at 6:45 p.m.

PROGRAM

Modern Crime Detection. Mr. Virgil Peterson, special agent in charge, Federal Bureau of Investigation, United States Department of Justice.

Subject to be announced at the meeting. Judge George C. Sweeney, United States District Court.

EVANS MEMORIAL HOSPITAL

A research conference will be held in the Evans Auditorium, 78 East Concord Street, on Wednesday, December 18, at 5 p.m. Dr. Harold J. Jeghers will speak on "Recent Developments in Vitamin Therapy."

MASSACHUSETTS MEMORIAL HOSPITALS

There will be a staff meeting of the Massachusetts Memorial Hospitals in the Evans Memorial Auditorium on Friday, January 3, at 8:15 p.m. Dr. Howard M. Clute will be the chairman.

PROGRAM

Presentation of Acute Small-Bowel Obstruction Cases. Dr. Ralph Zupanec.

Real and Suspected Acute Intestinal Obstruction. Dr. Leland S. McKittrick.

Discussion of Enterostomy in Acute Intestinal Obstruction. Dr. Howard M. Clute.

DANVERS STATE HOSPITAL

There will be a clinicopathological conference of the Danvers State Hospital, Hathorne, in the nurses' home of the hospital on Friday, December 27, at 8:30 p.m. Dr. John D. Stewart, of Boston, will speak on "Jaundice."

THIRD ANNUAL CONGRESS ON INDUSTRIAL HEALTH

The third annual Congress on Industrial Health, sponsored by the American Medical Association, will be held on Monday and Tuesday, January 13 and 14, at the Palmer House, Chicago. This meeting is designed to acquaint the physician and others with the rapidly expanding importance of preventive medicine and surgery applied to industrial organization. Symposiums have been arranged to present the best current opinion on the management of industrial disability. The dinner and evening meeting on Tuesday, January 14, will be concerned with the relation of the private practitioner to the industrial health movement. On Wednesday, January 15, the Chicago Medical Society will conduct clinics illustrating practical problems in industrial medicine, industrial hygiene and traumatic surgery.

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION, INC.

The eighteenth annual meeting of the American Orthopsychiatric Association, an organization for the study and treatment of behavior and its disorders, will be held at the Hotel Pennsylvania, New York City, on February 20, 21 and 22, 1941. A registration fee will be charged for nonmembers.

Preliminary programs will be sent on request to the American Orthopsychiatric Association, Inc., 1790 Broadway, New York City.

MISSISSIPPI VALLEY MEDICAL SOCIETY 1941 ESSAY AWARD

The Mississippi Valley Medical Society offers a cash prize of $100, a gold medal and a certificate of award for the best unpublished essay on a subject of interest and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Entrants must be members of the American Medical Association. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society at Cedar Rapids, Iowa, October 1, 2 and 3, 1941, the society reserving the exclusive right to publish the essay in its official publication — the *Mississippi Valley Medical Journal*. All contributions must not exceed 5000 words, be typewritten in English in manuscript form, be submitted in five copies, and be received not later than May 1, 1941. Further details can be secured from Harold Swanberg, M.D., secretary, Mississippi Valley Medical Society, 209–224 W. C. U. Building, Quincy, Illinois.

COURSE ON THE WRITING AND EDITING OF SCIENTIFIC MANUSCRIPTS

A course of ten evening lecture-meetings on the writing and editing of scientific manuscripts is again offered by Mr. Tuckerman Day, formerly with the Harvard University Press, and now with the Riverside Press, Cambridge.

The meetings will be held on Mondays at 3 Joy Street, Boston, beginning in January, on a date to be announced.

This course is intended for writers, research workers, and secretaries and others interested in the preparation of manuscripts for publication. It aims to impart the following:

1. Increased ability to write clear, forceful and concise English.
2. A knowledge of the best modern editorial and typographical practices.
3. An acquaintance with printing-house methods and requirements.
4. An understanding of the relations among author, secretary, publisher and printer.

The charge for the course is $15.00, payable in advance. Each section will be limited to twenty members. Those wishing to enroll should write or telephone to Mr. Day at 26 Commonwealth Avenue, Boston (COM 7727), without delay.

Mr. Day was manuscript editor of the Harvard University Press for seven years and lay editor of the *New England Journal of Medicine* for four. He taught nonfiction writing for two years at the Boston Center for Adult Education. In addition to his evening classes, Mr. Day is now conducting a vocational course in manuscript writing at Radcliffe College.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING SUNDAY, DECEMBER 15

MONDAY, DECEMBER 16

12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

*8:15 p.m. New England Heart Association. Moseley Building. Massachusetts General Hospital.

TUESDAY, DECEMBER 17

*9–10 a.m. Clinical Significance of the Hypothalamus. Dr. Kurt Goldstein. Joseph H. Pratt Diagnostic Hospital.

12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital amphitheater.

WEDNESDAY, DECEMBER 18

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital.

*2–4 p.m. Malnutrition. Drs. Soma Weiss and J. E. Dunphy. Peter Bent Brigham Hospital.

5 p.m. Recent Developments in Vitamin Therapy. Dr. Harold J. Jeghers. Evans Memorial Hospital, research conference.

6:45 p.m. Massachusetts Society of Examining Physicians. Copley-Plaza Hotel, Boston.

*8 p.m. New England Society of Physical Medicine. Hotel Kenmore, Boston.

THURSDAY, DECEMBER 19

*8:30 a.m. Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital, at the Peter Bent Brigham Hospital.

*9–10 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.

FRIDAY, DECEMBER 20

*9–10 a.m. The Banti Syndrome. Dr. L. K. Diamond. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, DECEMBER 21

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

DECEMBER 27 — Danvers State Hospital, clinicopathological conference. Page 999.

DECEMBER 27–29 — National Convention of the Association of Medical Students, Boston.

JANUARY 3, 1941 — Massachusetts Memorial Hospitals, staff meeting. Page 999.

JANUARY 4 — American Board of Obstetrics and Gynecology. Page 787, issue of November 7.

JANUARY 9 — Pentucket Association of Physicians. Page 263, issue of August 15.

JANUARY 13, 14 — Third Annual Congress on Industrial Health. Page 999.

FEBRUARY 20–22 — American Orthopsychiatric Association, Inc. Page 999.

MARCH 8 — American Board of Ophthalmology. Page 201, issue of August 1.

APRIL 21–25 — American College of Physicians. Page 1065, issue of June 20.

MAY 21, 22 — Massachusetts Medical Society, Boston.

JUNE 2–6 — American Medical Association. Cleveland, Ohio.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH

JANUARY 8 — Visceral Pain and Its Relief. Dr. James C. White. Danvers State Hospital, Hathorne.

FEBRUARY 5 — Gastric and Duodenal Ulcer: Diagnosis and treatment. Dr. Arthur Allen. Lynn Hospital.

MARCH 5 — X-ray in Heart Disease. Dr. Merrill C. Sosman. Essex Sanatorium, Middleton.

APRIL 2 — Pediatric Problems in General Practice. Dr. Joseph Garland. Addison Gilbert Hospital, Gloucester.

MAY 14 — Relation of the Doctor to the Law. Mr. Leland Powers. New Ocean House, Swampscott.

FRANKLIN

JANUARY 14.

MARCH 11.

MAY 13.

Meetings will be held at 11 a.m. at the Franklin County Hospital, Greenfield.

NORFOLK

JANUARY 28 — Carney Hospital.

FEBRUARY 25 — Medicolegal meeting. 8:30 p.m. Hotel Puritan, Boston.

MARCH 25 — To be announced.

MAY 8 — Censors' meeting. Hotel Puritan.

SUFFOLK

JANUARY 29 — Page 604, issue of October 10.

APRIL 30 — Page 604, issue of October 10.

WORCESTER

JANUARY 8, 1941 — Worcester City Hospital, Worcester.

FEBRUARY 12 — Worcester State Hospital, Worcester.

MARCH 12 — Memorial Hospital, Worcester.

APRIL 9 — Hahnemann Hospital, Worcester.

Supper at 6:30 p.m. followed by a business meeting and scientific program.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Haemorrhoids and Their Treatment: The varicose syndrome of the rectum. By Kasper Blond, M.D. (Vienna), formerly first assistant, Rothschild Hospital, Vienna, and honorary consulting surgeon, Municipal Hospital, Vienna. Translated by E. Stanley Lee, M.S., F.R.C.S., honorary assistant surgeon, Westminster Hospital. 8°, cloth, 140 pp., with 49 illustrations. Baltimore: Williams and Wilkins Company, 1940. $4.50.

A Review of the Psychoneuroses at Stockbridge. Gaylord P. Coon, M.D., chief medical officer, Boston Psychopathic Hospital; and Alice F. Raymond, A.B., statistician, Department of Child Hygiene, Harvard School of Public Health. 8°, cloth, 299 pp., with 66 tables and 2 figures. Brattleboro, Vermont: E. L. Hildreth & Company, Incorporated, for Austen Riggs Foundation, Incorporated, Stockbridge, Mass., 1940. $2.00 (obtainable from the Foundation).

Synopsis of Materia Medica, Toxicology and Pharmacology. By Forrest Ramon Davison, B.A., M.Sc., Ph.D., M.B., assistant professor of pharmacology, School of Medicine, University of Arkansas. 12°, cloth, 633 pp., with 45 illustrations. St. Louis: C. V. Mosby Company, 1940. $5.00.

In Search of Complications: An autobiography. By Eugene de Savitsch, M.D. Foreword by Arthur Krock. 8°, cloth, 396 pp. New York: Simon and Schuster, 1940. $3.00.

Bacillary and Rickettsial Infections, Acute and Chronic: A textbook. Black Death to White Plague. By William H. Holmes, M.D., professor of medicine, Northwestern University Medical School, and chairman, Department of Medicine, Passavant Memorial Hospital, Chicago. 8°, cloth, 675 pp. New York: Macmillan Company, 1940. $6.00.

The Treatment of Diabetes Mellitus. By Elliott P. Joslin, M.D., Sc.D., medical director, George F. Baker Clinic, New England Deaconess Hospital, clinical professor of medicine emeritus, Harvard Medical School, and consulting physician, Boston City Hospital; Howard F. Root, M.D., physician, New England Deaconess Hospital, consultant in medicine, Eastern Maine General Hospital, Massachusetts State Infirmary, Tewksbury, and Middlesex County Sanatorium, and instructor in medicine, Harvard Medical School; Priscilla White, M.D., physician, New England Deaconess Hospital, and instructor in pediatrics, Tufts College Medical School; and Alexander Marble, M.D., physician, New England Deaconess Hospital, and instructor in medicine, Harvard Medical School. Seventh edition, thoroughly revised. 8°, cloth, 783 pp., with 117 tables. Philadelphia: Lea & Febiger, 1940. $7.50.

Diseases of the Urethra and Penis. By E. D'Arcy McCrea, M.D., M.Ch. (Dub.), F.R.C.S. (Eng.), honorary surgeon, Salford Royal Hospital, Manchester (England). 8°, cloth, 306 pp., with 181 illustrations. Baltimore: Williams & Wilkins Company, 1940. $6.50.

Psychiatry for the Curious. By George H. Preston, M.D., commissioner of mental hygiene for the State of Maryland. 8°, cloth, 148 pp., with 17 sketches. New York: Farrar & Rinehart, Incorporated, 1940. $1.50.